Author/s:
Sheers, Nicole Louise

Title:
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Date:
2020

Persistent Link:
https://hdl.handle.net/11343/253878

The effects of lung volume recruitment therapy on respiratory function and quality of life in people with neuromuscular disease

Nicole Louise Sheers

BPhysio(Honours), MPhysio

ORCID ID: 0000-0003-1847-4266

Doctor of Philosophy thesis: September 2020

Department of Medicine (Austin Health)

Faculty of Medicine, Dentistry and Health Sciences

The University of Melbourne

Submitted in total fulfilment for the degree of

Doctor of Philosophy

ABSTRACT

Respiratory muscle weakness results in substantial discomfort, disability and ultimately death in many neuromuscular diseases (NMDs). Respiratory compromise manifests as some or all of, shallow breathing, poor cough and associated difficulty clearing mucus, respiratory tract infections, hypoventilation, sleep-disordered breathing and chronic ventilatory failure. As survival outcomes improve for many NMDs, there is a shift towards more proactive and preventative chronic disease multi-disciplinary care models that manage symptoms, improve morbidity and reduce mortality. Unfortunately, clinical care guidelines for chronic NMD care are based largely on clinical rationale and consensus opinion rather than level A evidence. These guidelines typically recommend therapies to enhance lung inflation and cough effectiveness, however there is minimal evidence that performing techniques regularly is beneficial. Lung volume recruitment (LVR) is one such therapy. Simple, inexpensive and widely-accessible, it delivers air via a manual resuscitation bag to augment lung inflation above a person's own deepest breath. Given the absence of prospective controlled research, this thesis aimed to investigate the effect of regular LVR in people with NMD.

Firstly, a cross-sectional cohort study of 80 community-dwelling adults with NMD and respiratory system impairment identified that participants with slowly-progressive forms of NMD have smaller lung volumes and respiratory system compliance (C_{rs}) than participants with rapidly-progressive motor neurone disease, despite having a similar degree of respiratory muscle weakness. Stiffness was associated with smaller lung volume in long-standing NMD, supporting the hypothesis that maintaining lung volume and C_{rs} may ameliorate respiratory decline.

The second component of this thesis confirmed the feasibility of LVR; 95% of participants naïve to the therapy could successfully augment their lung insufflation capacity (LIC, the maximum inflation capacity obtained by assisting inflation). Moreover, LIC and C_{rs} increased following a single-session of LVR therapy. These immediate effects were only evident when naïve; when assessed three-months later there was no change in respiratory function following a single-session of LVR.

The third and primary component of this work, a randomised controlled trial of twice-daily LVR or an active control treatment for three-months, found a statistically significant difference in LIC between groups favouring LVR. No demonstrable change in lung volumes, respiratory muscle strength, symptoms or quality of life was found, suggesting a learning effect or acclimatisation to higher inflation pressures may be responsible for the increase. However, an improvement in C_{rs} predominantly in the LVR group means a beneficial effect on underlying respiratory mechanics cannot be excluded, especially if conducted for a longer duration. Notwithstanding the need for further longitudinal studies, the observed improvement in the primary outcome of LIC in the absence of apparent harm or burden, provides robust preliminary data supporting clinical recommendations and practice that regular LVR be performed by people living with NMD. The clinical significance of a higher LIC is still to be fully realised, but this thesis has demonstrated an effect that is compatible with the clinical and biologically-plausible rationale for this therapy.

GENERAL DECLARATION

I hereby declare that this thesis comprises only my original work towards the degree of Doctor of Philosophy, except where indicated in the Preface This thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis is fewer than the maximum word limit of 100 000 words in length, exclusive of tables, figures, legends, references and appendices.

Signed:

Nicole Sheers

Department of Respiratory and Sleep Medicine

Austin Health, Heidelberg, Victoria, Australia

University of Melbourne, Parkville, Victoria, Australia

2nd September 2020

PREFACE

All work contained in this thesis was performed by myself, except for the following:

Preparatory work in the respiratory laboratory was performed with the assistance and mentorship of Peter Rochford, Head Scientist, Department and Sleep Medicine, Austin Health.

Data were collected by myself, with assistance from Swinburne University undergraduate students. The following students undertook 12-month Industry Based Learning placements as a research assistant within our research team, co-supervised by myself: Carmel Nicholls, Sandra Henderson, Alyssa Rigoni and Krisha Saravanan. Ms Saravanan's talent as an artist was also employed to hand-draw the technical circuit illustrations that accompany this thesis (Section 4.3). In addition to these valued students, I also co-supervised physiotherapists from the Department of Physiotherapy on a rotational research placement, who conducted some of the follow-up assessments in participants' homes and assisted myself with baseline and final assessments. These physiotherapists: Rebecca Dirago, Phoebe Naughton, Marlena Ahrens, Megan Hawkins, Luke McDonald and Sarah Retica, also assisted with data management and administrative tasks crucial to supporting a research project.

Senior respiratory physiotherapists from the Victorian Respiratory Support Service, Linda Rautela and Caroline Chao, were the study's unblinded clinicians. They performed all participant and carer training of the allocated treatments at the initial assessment (Timepoint 0), and provided clinical support to the research assistants and/or research physiotherapists as needed.

As discussed in Section 4.5, Dr. Doug McKim and Joao Tomas from The Ottawa Hospital Rehabilitation Centre in Ontario, Canada developed and constructed the counter used to objectively measure lung volume recruitment therapy use. Their invention added a novel element to this trial.

ACKNOWLEDGEMENTS

Acknowledgement (n.): "the act of acknowledging; an expression of appreciation; a token of due recognition; a statement expressing the author's gratitude to others"

When a trusted and respected friend suggested that this PhD would be one of the hardest things that I would do, I underestimated the gravity of the pronouncement. Not because I was naïve to the work involved or possessed an inflated belief in my ability, but because I did not expect this journey to be as fulfilling, and therefore as hard, as it has been. The comment was not intended to dissuade me; if anything, I suspect it was said to induce me to commit to this official course of study. Clearly it worked, and I am indebted to Professor David Berlowitz for planting the seed and providing the appropriate amount of prodding to help me to reach this point.

I have been extremely fortunate to have had two attentive, magnanimous supervisors support me through this journey. David and Associate Professor Mark Howard have been generous with their time, guidance, advice and knowledge. They possessed a genuine interest in this project for its potential importance to people living with neuromuscular disease, and as an avenue for my professional growth, learning and development. I am incredibly privileged to have had their unwavering assistance, encouragement, trust and belief in my potential as a clinician researcher; their noble, gifted but different approaches to teaching rank alongside Obi-Wan Kenobi, and I thank them for mentoring this Padawan.

Throughout my life, I have been surrounded by a culture that respects and fosters inquisition and further learning. Without this environment I doubt whether I would be in this current position, and my parents Pam and Graeme deserve much of the credit. Coming from working-class backgrounds and having a young family, they did not have formal education opportunities in their early twenties, however both prioritised tertiary study in their adult lives. I was outraged to learn that my mum was forced by her parents to turn down a scholarship and was not allowed to finish her secondary

education, but wonder whether this drove her subtle feminism. Gender was not an issue in my childhood; the thought that I could not go to university, undertake a Masters or PhD never crossed my mind. Rather, being “independent” was the ethos in our home. They led by example, their perseverance and hard work are instilled in me, but without their support and love and that of my brother Craig, I would not have made the choices in life that I have. Thank you xx

Similarly, I have only ever worked in a workplace full of strong-willed colleagues and friends who modelled and valued enquiry. At a time when PhDs were uncommon in the public health arena, I watched four cardiorespiratory physiotherapy colleagues at the Austin Hospital embark down this path – all of whom I still look up to (but am no longer afraid of!). In addition to Catherine Hill, Anne Holland, Sue Berney and David, I have learnt from experienced, talented and caring clinicians that have shaped my practice, including Carolyn Peters, Linda Rautela and Jack Ross. The Austin has definitely moulded and nurtured me; in part this PhD signifies my appreciation, and I hope that I have and will continue to be a similar source of inspiration for other clinicians.

I would also like to thank my other Austin family, the Victorian Respiratory Support Service and Department of Respiratory and Sleep Medicine. Linda and Caroline Chao in particular have stood by my side throughout this research trial. They were always enthusiastic, bent-over-backwards to help the participants and research team on those lengthy assessment days, and did not begrudge me for stepping out of my clinical role to become a student. Along with Marnie Graco and Rachel Schembri, fellow PhD students at the Institute for Breathing and Sleep, they shared the day-to-day humdrum, celebrated the small wins with me, provided much-needed emotional support and friendship. Outside of the Austin, my good friend (and an inspiring clinician researcher) Jacqui Frowen did this and more; almost every Wednesday we would chat and debrief as our kids’ set about swimming lessons. It takes a village to raise a child, and these are just some of the special people who have helped me raise this baby.

I would also like to extend a special note of appreciation to Peter Rochford, Head Scientist of the Department of Respiratory and Sleep Medicine when I commenced my PhD. David knew me well enough to know that I needed a project that was steeped in respiratory physiology, and Pete devoted time to teach me some of the theoretical and practical skills I would need. The preparatory work and experiments we undertook in the lab were so much fun, in part because of the discussions with Pete about physiology (and every other topic) that always ended in banter. I am grateful that this process has indirectly provided the opportunity to develop relationships with these incredible colleagues. It is not what we do, but who we do it with that is important. You guys all rock.

Likewise, this project has enabled me to form collaborations with some very generous leaders in this field, including Michel Toussaint, Doug McKim and Sherri Katz. I appreciate the opportunity given by Michel to co-author a paper with him, which then led to an invitation to participate in the European Neuromuscular Centre international workshop on airway clearance techniques in people with neuromuscular disease, March 2017. His confidence in my clinical and research practice has been pivotal in my development as an emerging expert in this area, and reflects his gracious leadership and amity. The same sentiment and thanks applies whole-heartedly to Doug and Sherri, who invited David and myself to their investigators' meeting in Ottawa in January 2019. Their counsel, collegiality and friendship is valued and reciprocated.

As might be expected, this research could not have occurred without the financial support received from grants and funding bodies; I would like to thank the National Health and Medical Research Council, the Motor Neurone Disease Research Institute of Australia, the Institute for Breathing and Sleep and the Physiotherapy Research Foundation. In addition, the multitude of in-kind support provided by colleagues, the Department of Respiratory and Sleep Medicine and the Institute for Breathing and Sleep is immeasurable.

Notwithstanding the above support, it is the contribution of participants, their families and carers that continues to astonish me. I am forever grateful to the people who volunteered to take part in this trial, for their time, effort, commitment and hospitality. Over the course of this project, there were many times when I was moved to tears by the optimism, tenacity, openness and generosity of participants. Every participant was remarkable, embodied why I did this PhD and taught me something. In a parallel universe, I could imagine some being family friends or sharing dinner with them, because they are just such good people. Sadly, many of the people in this cohort are no longer alive, and I am overwhelmed that they entrusted me with their everlasting gift to science. I dedicate this work to them.

Finally, there are three people who deserve the greatest acknowledgement: Uyen, Ollie and Noah. Committing to a PhD was a family decision, but it was a complete no-brainer to Uyen that I should do this. Without his love and belief in me, unrelenting encouragement and tireless pragmatic support, I would not have commenced let alone completed this thesis. To my gorgeous Ollie and sweet Noah, thank you for indulging me. You boys (all three of you x) have been part of every step; you listened, understood and questioned, tolerated my absence and kept me grounded. You are my greatest loves, and have definitely earned the right to don the floppy hat.

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List of Abbreviations

ACBT	Active cycle of breathing technique
ALS	Amyotrophic lateral sclerosis
ALSFRS-R	Revised amyotrophic lateral sclerosis functional rating scale
AQoL-8D	Assessment of quality of life – 8D
ATP	Ambient temperature, pressure
AUC	Area under the curve
BiPAP™	Bilevel positive airway pressure
BMI	Body mass index
BTPS	Body temperature, pressure, saturated with water vapour
CCC	Concordance correlation coefficient
C_{cw}	Chest wall compliance
CI	Confidence interval
C_L	Lung compliance
CPAP	Continuous positive airway pressure
C_{rs}	Respiratory system compliance
CV	Coefficient of variation
DMD	Duchenne muscular dystrophy
E_{cw}	Chest wall elastance
EIT	Electrical impedence tomography
E_L	Lung elastance
E_{rs}	Respiratory system elastance
ERV	Expiratory reserve volume
FRC	Functional residual capacity
FVC	Forced vital capacity
HR	Heart rate
HRQoL	Health-related quality of life
IBAS	Institute for Breathing and Sleep

IC	Inspiratory capacity
ICC	Intraclass correlation coefficient
IPPB	Inspiratory positive pressure breathing
LIAM	Lung insufflation assist manoeuvre
LIC	Lung insufflation capacity
LMN	Lower motor neurone
LVR	Lung volume recruitment
MAC	Manually assisted cough
MAP	Mean arterial blood pressure
ME	Mechanical exsufflation
MEFV	Maximal expiratory flow-volume curve
MEP	Maximal expiratory pressure
MI	Mechanical insufflation
MIC	Maximum insufflation capacity
MID	Minimal important difference
MI-E	Mechanical insufflation-exsufflation
MIP	Maximal inspiratory pressure
MND	Motor neurone disease
NIV	Non-invasive ventilation
NMD	Neuromuscular disease
OR	Odds ratio
P_A	Alveolar pressure
P_{AW}	Airway pressure
PCF	Peak cough flow
PCF_{LIC}	Peak cough flow from lung insufflation capacity
P_{di}	Transdiaphragmatic pressure
PEF	Peak expiratory flow
P_{ga}	Gastric pressure

PICF	Participant information and consent form
P_L	Lung recoil pressure / transpulmonary pressure gradient
PLS	Primary lateral sclerosis
P_{mo}	Mouth pressure
P_{oes}	Oesophageal pressure
P_{pl}	Intrapleural pressure
PPS	Post-polio syndrome
P-V curve	Pressure-volume curve
QoL	Quality of life
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
RTI	Respiratory tract infection
RV	Residual volume
SCI	Spinal cord injury
SD	Standard deviation
SMA	Spinal muscular atrophy
SNIP	Sniff nasal inspiratory pressure
SRI	Severe respiratory insufficiency questionnaire
SVC	Slow vital capacity
TLC	Total lung capacity
UMN	Upper motor neurone
VC	Vital capacity
VCM	Volumetric cough mode
VPAP™	Variable positive airway pressure
VRSS	Victorian Respiratory Support Service
V_T	Tidal volume
WOB	Work of breathing

Units of Measurement

$ AUD	Australian dollars
cm	centimetres
cmH_2O	centimetres of water
cmH_2O/L/sec	centimetres of water, per litres per second
°C	degrees centigrade
Hz	hertz
kg	kilograms
kg/m²	kilogram per square metre
L	litres
L/cmH_2O	litres per centimetres of water
L/cmH_2O/L	litres per centimetres of water, per litre
L/min	litres per minute
L/s	litres per second
L/year	litres per year
mL	millilitres
mL/cmH_2O	millilitres per centimetres of water
mmHg	millimetres of mercury
ms	milliseconds
%	percent
%pred	percentage of predicted normal values

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1 THESIS OVERVIEW

1.1 RESPIRATORY ISSUES IN NEUROMUSCULAR DISEASE

Respiratory muscle weakness, shallow or laboured breathing, weak cough, inability to clear oral secretions or mucus, chest infections and/or sleep-disordered breathing are common consequences and complications many people living with a neuromuscular disease (NMD) experience. Respiratory impairment and the associated clinical manifestations cause discomfort and disability. Ultimately, respiratory failure is the leading cause of death for people with conditions such as motor neurone disease (MND), spinal muscular atrophy (SMA) and other muscular dystrophies.[1-3]

The cornerstone of management for respiratory failure is home mechanical ventilation, most commonly non-invasive ventilation (NIV). This is an effective therapy that, in people with MND, can slow the progression of respiratory muscle weakness and lung volume decline, improve symptoms of breathlessness and nocturnal hypoventilation, and prolong survival.[4-9] Treating hypoventilation and the resultant respiratory failure is a crucial aspect of the respiratory care of people with NMD, however there are also other aims. Reducing the effort of breathing, improving cough effectiveness, and preventing chest infections are likely to be of substantial benefit, but the role of NIV here is unknown. Furthermore, whilst maintaining lung volume or slowing the rate of decline is integral to improving survival, there may be other therapies in addition to NIV that also address this.

A growing number of consensus statements and disease-specific treatment guidelines include other respiratory therapies and suggest them as adjuncts to care.[10-17] Lung volume recruitment (LVR) is one such technique, whereby a resuscitation bag with a one-way valve is used to supplement the volume of air that can be breathed in. Consecutive bag compressions deliver positive pressure via a mouthpiece or mask, cumulating in an assisted inflation “deep breath”. Performing LVR can improve the expiratory airflow produced during cough,[18] potentially enhancing clearance of mucus. It may be beneficial during acute respiratory tract infections (RTIs) and has also been

recommended as a daily prophylactic routine, with the aim of maintaining lung and chest wall "flexibility", preventing RTIs and slowing respiratory system decline.

Much of the rationale for using LVR is based on clinical reasoning and extrapolation from other patient populations, as robust evidence of therapeutic efficacy in NMD has not yet been established. For example, in the intensive care unit hyperinflation manoeuvres similar to LVR are performed in intubated patients with heterogeneous medical conditions to inflate areas of under-expanded or collapsed lung and aid sputum clearance.[19-21] In the absence of disease-specific scientific evidence, it may be reasonable for clinicians to trial the use of respiratory therapies in other situations, if the goal of treatment is similar and there are no contraindications. However, instigating regular treatment has the potential to burden people living with NMD and their carers, hence clinical recommendations must also be evidence-based. If treatments are not efficacious, redirection of resources to other areas of health care may be justified. Furthermore, objective evidence of benefit and knowledge translation strategies are required if the wider population of people living with NMD are to have access to therapies, resources and suitably-skilled health professionals to assess, implement and monitor them.

1.2 OVERARCHING AIM

The aim of this thesis is to investigate the role for regular LVR therapy in people with NMD. Firstly though, a better understanding of the features of respiratory dysfunction in this population is necessary, in order to establish the rationale for treatment. Investigating the immediate physiological effect of LVR is also critical to determine the mechanisms by which longer-term LVR therapy may be beneficial and will constitute the second element of this project. The third and primary component of this work, a randomised controlled trial (RCT) comparing the use of LVR to an active control treatment twice a day for a three-month period, will address the broad aim.

1.3 THESIS STRUCTURE

Chapter Two of this dissertation will provide a précis of NMD including diagnoses relevant to this research, the healthy respiratory system and current understanding of respiratory dysfunction in people with NMD. With an understanding of these issues, respiratory management strategies will be discussed, focusing on LVR. Research aims and hypotheses will be presented.

Research project methodology will be detailed in Chapter Three, including study design, individual experiments, participants, treatments, outcome measures and study schedule. The measurement procedures, equipment used for data collection and other technical aspects will be defined in Chapter Four. One particularly relevant and novel component of this thesis, respiratory system compliance (C_{rs}), will be addressed separately in Chapter Five.

Respiratory function of participants with NMD at baseline will be presented in Chapter Six. Physiological outcome measurements, the relationships between these and having a prior RTI will be compared between people with rapidly-progressing MND and other more slowly-progressive conditions, to better understand the mechanisms underpinning the respiratory issues experienced by people living with NMDs. The immediate respiratory effects of a single-session of LVR in participants naïve to the therapy will be reported in Chapter Seven.

Chapter Eight will report the results of the three-month RCT of LVR versus the active control in people with NMD. Specifically, given the hypothesis that regular LVR may improve breathing capacity, cough, lung and chest wall flexibility, measures of lung volumes, cough peak expiratory flow and C_{rs} will be examined. The impact on symptoms and quality of life (QoL) will be explored, along with concordance with the prescribed therapies and dose-response. A study examining the immediate effects of a LVR in participants with prior exposure to the technique, will inform the interpretation of the RCT findings. Finally in Chapter Nine, these findings will be discussed in context of the overarching aim, with areas of future research identified.

2 BACKGROUND & LITERATURE REVIEW

2.1 NEUROMUSCULAR DISEASE

Neuromuscular disease is a broad term that encompasses diseases affecting the neuromuscular system, including upper motor neurones (UMN), peripheral nerves and other lower motor neurones (LMN, including fibres supplying neuromuscular spindles and muscle connective tissue), the neuromuscular junction or skeletal muscles.[22-26] Muscle function is impaired, resulting in weakness and atrophy. Hypertonia or hypotonia may also be associated with some diseases.

The World Federation of Neurology classifies NMDs according to the anatomical site of the lesion leading to weakness, and then pathogenesis (acquired or congenital).[27] Within this framework, diseases are classified as disorders of: i) motor neurones, ii) motor nerve roots, iii) peripheral nerve, iv) neuromuscular transmission or v) muscle (Table 2-1). The site of involvement, cause and rate of progression all influence the severity of impairment and prognosis; those NMDs that are associated with respiratory system involvement unfortunately have a poorer outcome than those that spare this region.

Site of lesion	Examples of diseases	Further sub-division
Motor neurones	Motor neurone disease (MND)	Amyotrophic lateral sclerosis (ALS) (UMN, LMN signs) ▪ Limb onset (cervical or lumbar onset) ▪ Bulbar onset ▪ Flail arm, flail leg (LMN initially) Primary lateral sclerosis (UMN) Progressive muscular atrophy (LMN)
	Spinal muscular atrophies (SMA)	SMA Types I – IV Kennedy SMA (bulbospinal atrophy)
	Viral disorders	Poliomyelitis Post-polio syndrome (PPS)
	Spinal cord injury (SCI)	
Motor nerve roots	Physical compression (e.g., trauma, disc prolapse, tumour)	Neurology specific to spinal cord segment → respiratory complications rare
Peripheral nerves	Genetic polyneuropathies	Charcot–Marie–Tooth syndrome
	Acquired polyneuropathies	Guillain-Barré syndrome
Neuromuscular transmission	Myasthenia gravis	
Muscle	Genetically determined myopathies	X-linked muscular dystrophies: ▪ Duchenne muscular dystrophy (DMD) ▪ Becker muscular dystrophy Autosomal muscular dystrophies: ▪ Facioscapulohumeral muscular dystrophy ▪ Limb girdle muscular dystrophy ▪ Bethlem myopathy

Site of lesion	Examples of diseases	Further sub-division
Muscle continued	Genetically determined myopathies continued	Myotonic disorders: ▪ Myotonic dystrophy Childhood myopathies: ▪ Congenital myopathies ▪ Nemaline myopathy
	Acquired myopathies	Inflammatory myopathies: ▪ Polymyositis ▪ Inclusion body myositis
	Metabolic myopathies	Includes hereditary glycogen, mitochondrial or lipid storage diseases (e.g. Acid maltase deficiency (Pompe's disease)

Table 2-1: Classification of neuromuscular diseases

UMN = upper motor neurone, LMN = lower motor neurone
Information compiled from: Neuromuscular Diseases: A Practical Approach to Diagnosis and Management. 3rd ed. 1997.
Chapter 5: Classification of Neuromuscular Disease, Swash and Schwartz.[27]

Clinically, these heterogeneous groups of NMDs are often considered in terms of rate of progression. Motor neurone disease is the most common adult-onset rapidly-progressive NMD; weakness spreads through a fully developed body, eventually affecting bulbar, respiratory and limb muscles. People with MND may have other pre-existing medical conditions or normal age-related changes, however the age at disease onset and rapidity distinguish MND from other progressive NMDs. These other NMDs largely have a childhood and/or slower onset, providing time for secondary complications to develop.

The heterogeneity within NMD and rarity of individual diagnoses favours categorising conditions with common characteristics for clinical and research purposes; commonly cohorts compromise rapidly-progressive, slowly- or non-progressive, variably-progressive diseases and "other" groups.[28,29] For this research project, two disease sub-groups were adopted: "MND", referring to rapidly-progressive MND, and "Other NMD", incorporating all other NMDs including restrictive chest wall disease. The incidence, prevalence and features of some of these individual diseases are described below.

2.1.1 MOTOR NEURONE DISEASE

Motor neurone disease is a rapidly-progressive, fatal neurodegenerative disease characterised by loss of UMNs and LMNs. Whilst the exact worldwide incidence is not known, in Europe the incidence is 2.16 per 100,000 person-years.[1] Familial MND accounts for 5-10% of cases, with the majority of cases being sporadic. Mutations of the gene superoxide dismutase-1 (*SOD1)* have been found in both familial and sporadic forms, with additional genes including *C9orf72* also implicated in the familial phenotype.[30,31] Advances in determining the cause of these genetic mutations and the pathogenesis of MND have been significant in recent years, yet curative treatments for MND are not within reach.

Motor neurone disease was previously regarded as occurring in three distinct forms: amyotrophic lateral sclerosis (ALS), progressive bulbar palsy and progressive muscular

atrophy. A fourth, rare but related disorder of primary lateral sclerosis (PLS) also exists. The first three sub-groups are now considered variations of the same disease process, with severe muscular atrophy reflecting anterior horn cell disease (LMN involvement), and spasticity and hyperreflexia indicating corticospinal tract lesions (UMN). Amyotrophic lateral sclerosis is the more common presentation and involves UMNs and LMNs. Progressive bulbar palsy produces predominantly UMN signs whereas progressive muscular atrophy is the least common of the three and is characterised by LMN involvement without definite evidence of UMN signs. Frontotemporal lobar degeneration is another characteristic feature with variable expression across the spectrum of MND. Within Australia, the clinical phenotypes of global ALS, flail arm, flail leg and PLS are used.[32] The global ALS phenotype demonstrates mixed UMN and LMN signs, and is further divided into bulbar, cervical or lumbar symptom onset phenotypes. Flail limb (arm and leg) phenotypes exhibit LMN signs, whereas PLS is an UMN-only variant associated with longer survival.

Median survival from symptom onset is between 20 to 48 months, although differences exist between the clinical phenotypes and at least 5-10% of patients live beyond a decade. People with global ALS have a more rapid progression compared to the flail or PLS phenotypes, and within ALS those with bulbar symptom onset have shorter survival times.[32] Age appears a strong prognostic factor, with older age at symptom onset correlated with reduced survival time. Management by a specialist MND centre with multidisciplinary care teams has demonstrated a positive effect on survival.[33]

2.1.2 SPINAL MUSCULAR ATROPHY

Spinal muscular atrophies are characterised pathologically by degeneration of the anterior horn cell, resulting in muscle wasting and atrophy. Distal SMA or hereditary motor neuropathy is a slowly-progressive form resulting in distal limb weakness and atrophy, with minimal respiratory complications. Proximal SMA is generally associated with more severe impairment and infant or childhood onset, although an adult-onset form (Kennedy's disease) does exist. The most common cause of proximal SMA is a

mutation on the *SMN1* gene; non-*SMN1*-related SMA accounts for <5% of infantile SMA.[34] *SMN1*-related SMA is due to an autosomal recessive genetic defect, with an incidence of 1 in 11,000 live births and a carrier frequency of 1 in 40-67 adults. Four types of *SMN1*-related SMA have been classified, based on attainment of clinical milestones.

1. Type I (Acute infantile, Werdnig-Hoffmann disease)

Disease begins in utero to first 6 months of life, is rapid, severe and fatal. Type 1 SMA is characterised by hypotonia, marked trunk and proximal limb weakness, an inability to roll or sit, impaired bulbar function, aspiration pneumonia, hypoventilation and respiratory failure. Life expectancy is usually less than 2 years, however milder SMA Type I cases have been known to live into adolescence with appropriate respiratory support (8% survival probability at age 10).[2]

2. Type II (Intermediate SMA)

Age of onset is generally from 6 to 18 months of age. Children with this phenotype sit independently but are never able to stand and walk. Lower limbs are more affected than upper limbs and respiratory muscle weakness is a major concern. Involvement of the paraspinal muscles can contribute to scoliosis. Life expectancy is varied depending on respiratory system involvement and may be reduced but people with Type II SMA often live into adulthood (77% survival probability at 20 years).[2]

3. Type III (Mild SMA, Kugelberg-Welander disease)

Presents in infancy or childhood, after the age of 18 months. Weakness develops in lower limb muscles usually after gait has been attained, but loss of independent gait in later life can occur. Respiratory muscle involvement is less of a feature and life expectancy is near to normal.

4. Type IV (Adult-onset SMA)

Begins after the age of 15 years, with a median onset of 35 years. Relatively mild, slowly-progressive weakness occurs in proximal limb muscles. Respiratory system involvement is rare, and life expectancy normal if the respiratory system is spared.

Kennedy's disease is another form of SMA, specific to males. It affects LMNs including those that arise from the brainstem to innervate the bulbar muscles. Age of onset is broad (between 20-60 years of age), and is characterised by slowly-progressive muscular weakness, usually affecting proximal spinal muscle and bulbar muscles before slowly progressing to distal limb muscles. Respiratory muscle involvement may be present and life expectancy is normal or slightly reduced.[35]

Major advances in the pharmaceutical treatment of SMA have been made in recent times. In 2017, results of two trials were published: a RCT investigating a repeated-dose intrathecally-administered antisense oligonucleotide (nusinersen),[36] and a cohort study of a single-dose gene replacement therapy.[37] In particular, the results of the nusinersen trial and subsequent clinical use is expected to change the Type I SMA disease course. Nusinersen-treated infants have gained head control, ability to roll, sit and in some cases stand, however the impact on respiratory muscle function is not yet known. In Australia, nusinersen is available for children with Type I or II SMA and it is anticipated that the need for invasive or NIV and airway clearance techniques (ACT) in this "treated-SMA" category will increase significantly.[34]

2.1.3 POLIOMYELITIS AND POST-POLIO SYNDROME

Poliomyelitis (polio) is an acute viral infection that can result in selective, rapid and irreversible degeneration of anterior horn cells and brainstem nuclei. Paralytic polio is classified into spinal, bulbar and bulbospinal forms, and in <10% of cases results in weakness of respiratory muscles.[38] In Australia, routine polio vaccination was introduced in 1956, with the last epidemic from 1961-1962,[39] however there remain people in their 60s with lasting paralysis. Furthermore, people with a previous history of poliomyelitis can develop a secondary condition known as post-polio syndrome (PPS). This is a clinical diagnosis, characterised by late-onset muscle weakness in skeletal or bulbar muscles. Weakness develops approximately 30 years later in both previously affected muscles and regions thought not to have been originally involved, and can be slowly-progressive.[35]

Although the aetiology of PPS has not been definitively established, it may be due to a gradual loss of remaining muscle fibres as a result of aging. The original infection depletes anterior horn cells with the residual anterior horn cells compensating by maximally re-innervating remaining motor units via axonal sprouting. It is hypothesised that these cells may age quicker due to earlier damage or increased metabolic demand associated with their compensatory role.[40]

2.1.4 DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is a X-linked recessive disease, characterised by a defect in the *dystrophin* gene that produces the protein dystrophin. Whilst the majority of cases are hereditary, approximately 30% are spontaneous mutations. As with other muscular dystrophies, it is primarily a disease of muscle, not the nervous system. Birth prevalence is reported as between 15.9 to 19.5 per 100,000 live births.[41]

Becker muscular dystrophy is a variant of DMD; genetically similar but with considerably improved prognosis. Whereas dystrophin is absent in DMD, in Becker muscular dystrophy it is present but structurally abnormal. This results in much milder muscle degradation and clinical symptoms. Consequently, it is often detected later in childhood, although it can still result in respiratory muscle involvement.

Dystrophin is present in the periphery of the muscle fibre, binds to actin filaments and a large complex of glycoproteins that spans the cell membrane of the muscle fibre (sarcolemma). The dystrophin-glycoprotein complex provides a structural link between the sarcolemma and the extracellular matrix, hence absence of dystrophin leads to defects in the tubular sheath that encases skeletal muscle. Defects in the membrane allow entry of extracellular fluid and calcium into the muscle fibre with a resultant increase in muscle protein degradation. As muscle fibres are lost, residual fibres become haphazardly arranged. A defective regeneration process also contributes to continuous degeneration of muscle fibres, fibrosis and pseudohypertrophy of muscle, which are the clinical signs characteristic of DMD. Cardiomyopathy features

prominently in the disease, occurring in approximately 80% of cases, as dystrophin and the dystrophin-glycoprotein complex are also present in smooth muscle.[42]

The prognosis of DMD has improved significantly over the past few decades. In a long-term, retrospective cohort study, median survival was reported as 25.8 years if born between 1955 and 1969. However this increased to 40.9 years for patients born after 1970, attributable primarily to advances in ventilation, with mention of other medical treatments such as steroid therapy and cardiac management.[43]

Duchenne muscular dystrophy is one type of muscular dystrophy; other genetic NMDs similarly cause abnormal expression of genes that modulate protein production necessary for muscle function. Deficiencies in other organelles within muscle fibres can also cause muscle dysfunction; mitochondria, glycogen and lipids provide metabolic support to the myofibrils and are depleted in metabolic myopathies.[44] Whilst a review of other myopathies and muscular dystrophies is beyond the scope of this thesis, specific diagnosis will be described in the participant cohort.

2.1.5 MYOTONIC DYSTROPHY

Myotonic dystrophy is an inherited, autosomal dominant, multi-system disorder characterised by myotonia (persistent contraction of muscle after the cessation of voluntary contraction). This phenomenon is due to increased instability of the muscle fibre membrane leading to repetitive firing from a single stimulus. Abnormal acetylcholine-gated channels in the cell membranes result in a lower resting membrane potential, and hence smaller changes in ion conductance are required for depolarisation.[45]

Age of onset is usually in the twenties, and the presentation is varied in terms of severity and distribution due in part to the multi-organ abnormalities. Patients often present with cataracts, ptosis or a characteristic facial appearance. Wasting and weakness of skeletal muscle usually begins in the distal muscles and slowly progresses to proximal limb and trunk muscles. Respiratory muscle weakness is a common later feature, contributing to reduced life expectancy. Smooth muscle involvement

commonly leads to cardiac abnormalities such as heart block, arrhythmias and cardiomyopathy, as well as problems with oesophageal, gastro-intestinal motility and dysphagia. Hypothyroidism and diabetes ensue due to endocrine involvement. Cognitive impairment may also be a characteristic present in people with myotonic dystrophy.[45]

2.1.6 RESTRICTIVE CHEST WALL DISEASE

Restrictive chest wall disease is a term that encompasses diseases that result in restriction of the thoracic cage. These can be classified as neuromuscular or mechanical in nature, and as such are often considered alongside each other, especially when respiratory dysfunction, hypoventilation and chronic respiratory failure are present.[46]

Neuromuscular diseases, particularly those of childhood onset such as DMD, SMA and poliomyelitis can result in secondary scoliosis and/or chest wall deformity due to muscular imbalances during growth. Chest wall disease secondary to long-standing quadriplegia, childhood spinal cord tumours and paraplegia are likewise neurological in origin, however others such as idiopathic or congenital scoliosis, McCune-Albright syndrome, Pterygium syndrome and osteogenesis imperfecta are primarily skeletal disorders.

2.2 RESPIRATORY INVOLVEMENT IN NEUROMUSCULAR DISEASE

Clinically, the inability to take a deep breath is the hallmark sign of many NMDs, measured as a fall in vital capacity (VC), the greatest volume of air that can be expelled after taking the deepest possible breath in.[47]

The mechanics of breathing during wakefulness and sleep are complex, and there are numerous reasons why this population may experience problems: i) respiratory muscle weakness may result in an inability to take deep breaths and predispose one to daytime and nocturnal hypoventilation and/or sleep-disordered breathing; ii) chronic under-breathing may lead to secondary stiffness of the ribcage, spine or thorax, further impeding respiration; and iii) weakness of the respiratory, swallowing and speech muscles could compromise cough and airway protection.

Sleep is a substantial challenge to breathing. Sleep onset in healthy individuals is associated with diminished afferent input to the respiratory control centre, in turn altering efferent output; behavioural influences cease with the loss of wakefulness, and metabolism and chemoreceptor sensitivity decrease. Upper airway muscle activity is also reduced during sleep, increasing airway resistance. Generalised skeletal muscle atonia during rapid-eye movement sleep results in inhibition of the intercostal and accessory muscles, thereby leaving the diaphragm as the sole muscle of inspiration.[9,48-50] Additionally, change from the upright to supine position decreases lung volumes, increases the intrathoracic accumulation of blood and alters the caudal gravitational pull on the intra-abdominal organs, displacing the diaphragm cranially into the ribcage and causing a drop in VC.[51] In a person with respiratory muscle weakness, these normal physiological disturbances become more pronounced. With increasing diaphragm weakness the fall in supine VC becomes greater[52] and the loss during rapid-eye movement sleep of compensatory inspiratory muscle activity more deleterious. If left untreated and/or in severe relentless disease, nocturnal hypoventilation and hypercapnia result, leading to daytime hypoventilation. As such, respiratory failure is the usual cause of death in many NMDs including MND[1] and muscular dystrophy.[3]

Respiratory complications such as alveolar collapse, mucus plugging and recurrent RTIs are also presumed to be significant clinical problems stemming from the inability to take a deep breath.[10] Chest wall restriction secondary to scoliosis or kyphoscoliosis may also impact on respiratory function; prior to the use of glucocorticosteroids in DMD, nearly all patients developed scoliosis in the second decade of life.[53] It is unclear whether scoliosis is mitigated or simply delayed now that the life expectancy of a person with DMD[54] and other congenital NMDs has increased, but certainly current adults with DMD, Type II SMA, other childhood-onset muscular dystrophies and PPS may have restrictive chest wall disease in addition to respiratory muscle weakness.

Involvement of the bulbar muscle group can also compromise respiratory function. Approximately 20-30% of people with MND have the bulbar-onset phenotype, and the vast majority of all those with MND develop bulbar symptoms as the disease progresses.[55] Bulbar muscle dysfunction can also occur in SMA, myotonic dystrophy, PPS and in the later stages of DMD.[54] Consequences of bulbar muscle involvement include dysphagia, aspiration of oral secretions and/or food, dysarthria and weak or poorly coordinated movement of the vocal cords (glottis). Cough may be affected; as will be discussed later, coordinated opening and closing of the glottis is important for this function. Whilst difficulty clearing sputum secondary to changes in airway cilia or mucus rheology is uncommon in NMD, mucus consistency can be affected secondary to aspiration of oral secretions, or dehydration. The accumulation and drooling of saliva (sialorrhoea) is reported in almost 50% of people living with MND, and generally attributed to poor saliva control or pooling secondary to weakness and spasticity in the tongue, facial and pharyngeal muscles.[56]

Surprisingly given these potential respiratory complications, the prevalence of respiratory issues in people living with NMD is poorly quantified. A large population-based cohort study conducted in the province of Ontario, Canada provides the best estimate, and suggests that a third of all people with a NMD may have respiratory system involvement. Like Australia, Canada has a universal public health care system; in Ontario, multiple administrative health databases also contain anonymised data for all province residents. From these, a cohort of all adults with a diagnosis of a NMD

over a 5-year period was identified and their health care utilisation over a minimum 7-year period collated. Thirty-five percent of the 185,586 people were known to a respiratory specialist, 33% performed respiratory function tests at least once and 5% were prescribed domiciliary home mechanical ventilation or continuous positive airway pressure (CPAP) for treatment of sleep-disordered breathing. Including the two-thirds of the population who did not require specialised respiratory care, individuals with NMD presented to an emergency department 1.6 times every 3 years for respiratory causes, with most of these requiring hospital inpatient admission (1.4 times per 3 years).[28]

Prior to detailing the elements of respiratory impairment and impact on respiratory function that people with NMD may experience, it is valuable to review the muscles involved in respiration and normal mechanics of breathing.

2.3 RESPIRATION AND COUGH IN A HEALTHY POPULATION

2.3.1 MECHANICS OF BREATHING

The primary role of the respiratory system is gas exchange. The conducting airways (trachea, bronchi and bronchioles) act as conduits within the lung, delivering inspired air to the respiratory zone. Respiratory bronchioles, alveolar ducts and alveolar sacs provide the gas exchange surface where diffusion occurs. In the conducting airways, pressure gradients are responsible for the movement of gas; these are created by the interplay between the lungs and chest wall of the thorax, with air flowing from a point of high pressure to one of low pressure.[57]

At the resting point of the respiratory cycle, zero airflow occurs and the lungs contain a resting volume of air known as the functional residual capacity (FRC). At FRC there is an equilibrium between the tendency of the lung tissue to recoil inward and the chest wall to spring outward. These two oppositely directed elastic recoil forces create a sub-atmospheric ("negative") pressure within the intrapleural space (intrapleural pressure, P_{pl}). The difference between pressure in the alveoli (alveolar pressure, P_A) and P_{pl} results in a transpulmonary pressure gradient across the lung tissue, also known as lung recoil pressure (P_L).

The respiratory cycle commences with contraction of the muscles of inspiration (Section 2.3.2), causing an increase in the volume of the thoracic cavity (Figure 2-1). This outward expansion of the chest wall takes with it the attached parietal pleura, resulting in a more negative or lower P_{pl}. The transpulmonary pressure gradient is widened, causing distension of the lung tissue across this high to low pressure system. As the thoracic volume increases by this movement of visceral pleura and lung tissue, P_A will drop below atmospheric pressure. Another pressure gradient is created between the airway opening (i.e., mouth pressure, P_{mo}) and the alveoli, causing in-flow of gas and hence inspiration. Once active expansion of the chest wall during inspiration ceases, the lungs return to their equilibrium position due to elastic recoil. Thus, under normal circumstances and quiet tidal breathing, expiration is a passive process.[57]

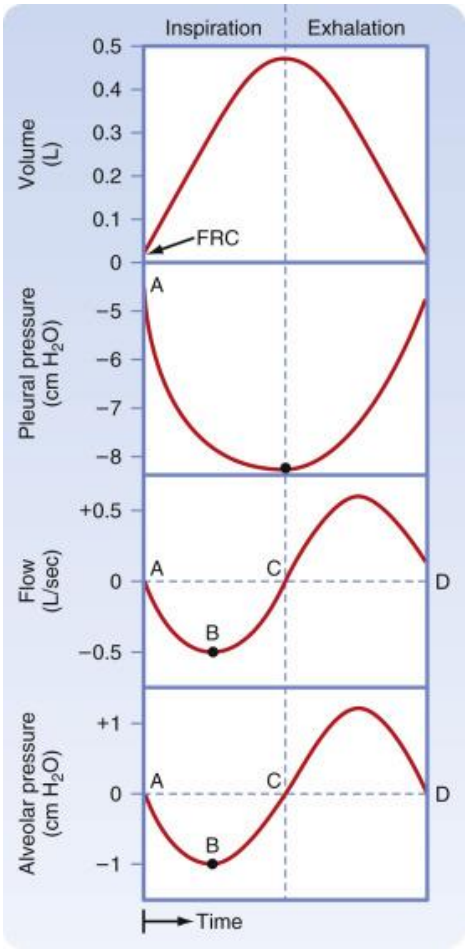

Figure 2-1: The respiratory cycle: volume, pleural pressure, flow and alveolar pressure during quiet breathing

From *Berne and Levy Physiology*. 7th ed. 2018. Chapter 21: Static Lung and Chest Wall Mechanics, Koeppen and Stanton.[58]

Whilst muscle strength is a major determinant of respiration and the resultant lung volume, the elastic, resistive and inertial properties of the lung and chest wall also play an essential role. Stiffness of the respiratory system will alter recoil forces, meaning more muscle force is required to generate movement of the thoracic cavity. Alternatively, the same muscle force will generate less movement.

For respiration to occur during quiet restful breathing, the respiratory muscles, lung and chest wall must work in unison to change pressures and generate an inhaled and exhaled tidal volume (V_T) (Figure 2-2). Greater respiratory effort will result in larger volume changes; the maximum volume of gas that can be inspired from FRC is referred to as the inspiratory capacity (IC). Expiratory reserve volume (ERV) refers to the volume of gas that can be maximally exhaled from FRC. Together, IC and ERV constitute VC. The volume of gas remaining in the lungs and airways after a maximal exhalation is defined as the residual volume (RV). Total lung capacity (TLC) is the volume of gas in the lungs and airways after maximal inspiration, or the sum of all volume compartments (IRV + V_T + ERV + RV).[47,59]

As will be detailed in Section 2.4, the most common sequela of respiratory system involvement in NMD is a reduction in lung volume (lung volume restriction).

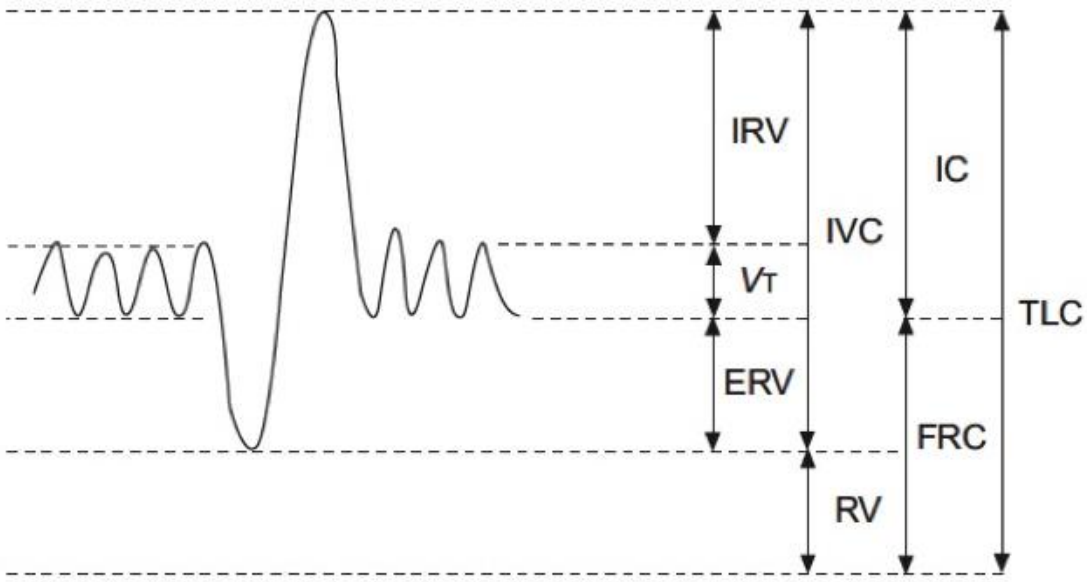

Figure 2-2: Static lung volumes and capacities

Schematic representation based on a volume-time spirogram
IRV: inspiratory reserve volume, V_T: tidal volume, ERV: expiratory reserve volume, IVC: (inspiratory) vital capacity, RV: residual volume, IC: inspiratory capacity, FRC: functional residual capacity, TLC: total lung capacity.
From Wanger *et al.* Standardisation of the measurement of lung volumes. 2005.[47]

2.3.2 MUSCLES OF RESPIRATION

Effective and efficient ventilation requires synchronised activation of motor neurones at the precise timing and intensity to multiple muscles. Respiratory muscle activity must occur in conjunction with that of upper airway muscles such as the genioglossus in order to maintain a patent path for airflow. Furthermore, the neural control of respiratory muscles is unique in that it can be both automatic or voluntary (via the bulbospinal and corticospinal pathways respectively).[60]

Respiratory muscles are histologically and physiologically identical to other skeletal muscles in the body. The primary inspiratory muscle of respiration, the diaphragm, is supported by the external intercostals, parasternal intercostals, scalene and sternocleidomastoid muscles (Figure 2-3). The diaphragm is comprised of a peripheral muscle sheet converging into a central aponeurosis, called the "central tendon". The muscle fibres are grouped into a crural portion that originate from the lumbar spine, and a costal portion that attach to the xiphoid process of the sternum and the upper margins of the lower ribs. These fibres attach to the inner surface of the ribcage and constitute a region known as the "zone of apposition".

Upon contraction of the diaphragm, the central tendon moves caudally, causing descent of the dome shape, expansion of the thoracic cavity downwards and displacement of the abdominal viscera. The cranial-dorsal orientation of the costal fibres produces two actions that combine to expand the lower portion of the ribcage. The fibres running along the inner surface of the ribs create an "insertional" force, lifting the lower ribs cranially. This would seem to oppose the desired caudal movement, except that it combines with a second "appositional" component. The increase in abdominal pressure caused by the caudal movement of the diaphragm is transmitted via muscle fibres attached to the zone of apposition, effectively pushing the lower ribs laterally. Furthermore, the cranial force of the lower ribs is transmitted, via the ribcage and sternum in a principle known as "interdependence" to the upper ribs, resulting in apical expansion of the upper chest and adding to the expansion of the thoracic cavity.[61,62]

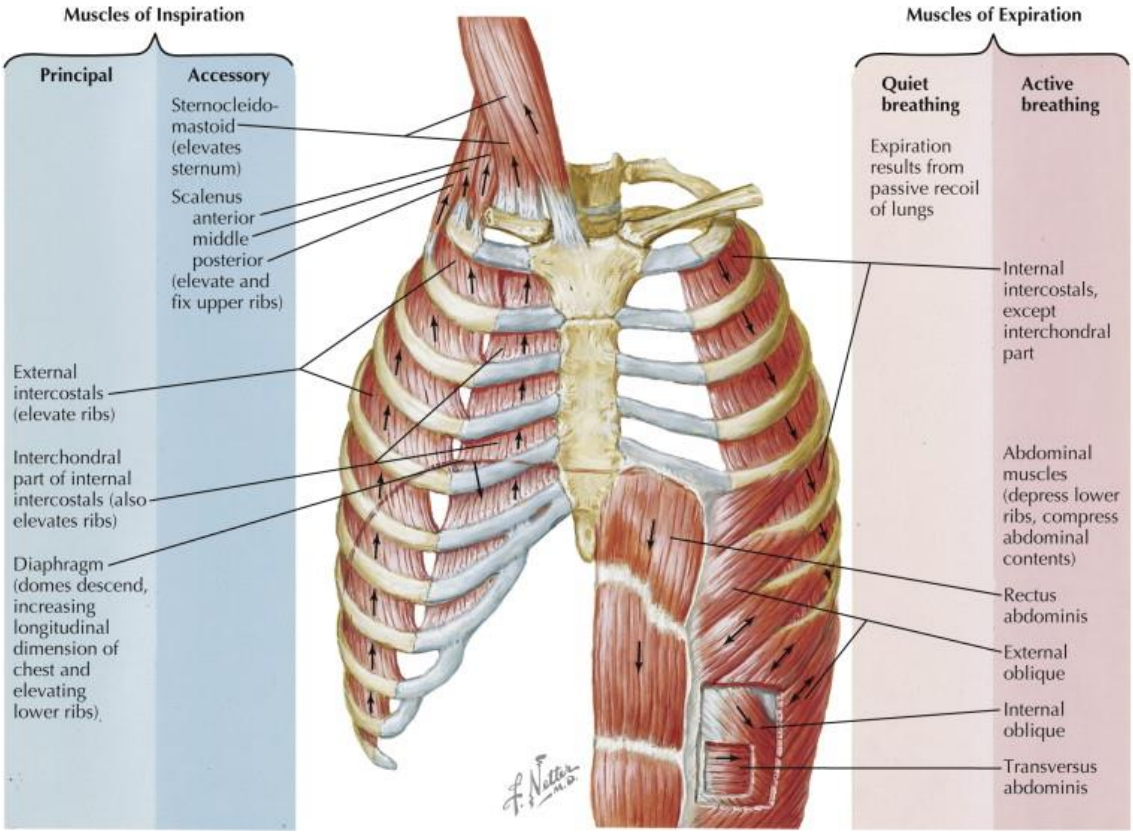

Figure 2-3: Muscles of respiration

From *Netter's Essential Physiology*. 2nd ed. 2016. Chapter 15: The Mechanics of Breathing, Mulroney and Myers.[63]

However, the diaphragm's role in this cranial expansion of the upper ribcage is minor compared to the action performed by the accessory muscles, namely the external intercostals. These muscle fibres have an oblique course, running downward and anteriorly to the adjacent, inferior rib. Muscle contraction lifts the rib horizontally and increases both the lateral and anterior-posterior ribcage diameters. This inspiratory mechanical advantage is greatest in the posterior sections of the lowest ribs and in fact becomes an *expiratory* mechanical advantage in the anterior portions of the most caudal rib spaces.[64] There are subtle differences in the timing and intensity of firing of these muscle fibres, such that different segments of intercostals are activated at different parts of the inspiratory cycle.[65] Furthermore, the interaction between the diaphragm and these additional muscles of inspiration is synergistic and occurs in a

coordinated manner. Contraction and subsequent elevation of the ribs at a time when the diaphragm is contracting caudally acts to prevent shortening of the diaphragm muscle, hence increasing its ability to generate pressure by maintaining it within an optimal range on a length-tension curve. Due to an origin-insertion pattern that runs between adjacent ribs, these accessory muscles of respiration also stabilise the ribcage, prevent distortion and any paradoxical inward motion that may otherwise occur due to the drop in intrathoracic pressure produced by the increase in thoracic volume.[66]

Other respiratory muscles include the parasternal intercostals (i.e., the interchondral part of the internal intercostals), sternocleidomastoid and the scalenus fibres. The parasternal muscles run caudally and posteriorly between the sternum and the chondrocostal junction. Acting during quiet inspiration, they raise the sternum[64] and increase the lateral diameter of the ribcage.[67] Contraction of the scalene group or sternocleidomastiod is similarly associated with a marked cranial displacement of the sternum and increase in the anterior-posterior dimension of the ribcage. Along with the parasternal intercostals, the scalenes are always active during tidal breathing inspiration in healthy humans;[64] as such these muscles are considered primary muscles of inspiration working in concert with the diaphragm.[68] Sternocleidomastoid however, is active only during occasions of increased inspiratory load in healthy people. All three muscle groups (parasternal intercostals, scalene and sternocleidomastoid) coordinate these respiratory functions with the non-respiratory movements of the trunk or neck they also produce.[65]

The four abdominal muscles, rectus abdominis, external oblique, internal oblique and transversus abdominis, demonstrate persistent, tonic abdominal contraction during inspiration. This maintains the increase in abdominal pressure caused during diaphragm descent. Without this bracing, the abdominal contents would displace forward, the dome of the diaphragm would descend and the zone of apposition between the inner aspect of the lower ribcage and the costal sections of the diaphragm would decrease in size. The inspiratory force generated by the diaphragm would be significantly reduced. However, with abdominal contraction and the

associated increase in abdominal pressure, the dome shape of the diaphragm is maintained for longer during inspiration, optimising the length-tension properties of the diaphragm and thus the force it can generate.[69]

The inward pull of these abdominal muscles and subsequent increase in abdominal pressure also produces a cranial displacement of the diaphragm. This could produce two opposite effects, depending on timing and state of other structures within the respiratory system. If it occurs immediately prior to inspiration, the zone of apposition and passive diaphragm tension increases, augmenting the force-generating capabilities of the primary inspiratory muscle and expanding the lower ribcage, similar to the insertional force of an active diaphragm contraction. However if the airway is open, this cranial movement will decrease lung volume, for example during forced expiration.[70]

2.3.3 RESPIRATORY SYSTEM COMPLIANCE

Respiratory system compliance (C_{rs}) refers to the distensibility of the respiratory system, specifically the change in volume generated by a change in pressure (**Equation** 1). Low compliance reflects a system that is stiff and more difficult to inflate. Compliance is the inverse of elastance, defined as the propensity of an object to return to its natural resting position, hence a system with low compliance has high elastic recoil.

$$Compliance = \frac{\Delta\ Volume}{\Delta\ Pressure}$$

$$Elastance = \frac{1}{Compliance}$$

Equation 1: Compliance and Elastance

Compliance of the respiratory system is comprised of two components; lung compliance (C_L) and chest wall compliance (C_{CW}). Being separate structures, the lungs and chest wall have different compliance characteristics, although only in a theoretical framework do they act in isolation. The histological composition of elastin and collagen fibres within lung tissue are primary determinants of C_L, whereas the intercostal muscles, connective tissue, ligaments and other structures of the sternocostal, costotransverse, costoverterbal joints and osteocartilaginous chest wall determine C_{CW}. The pressure-volume behaviour of these two components governs the compliance of the respiratory system as a whole (Figure 2-4).

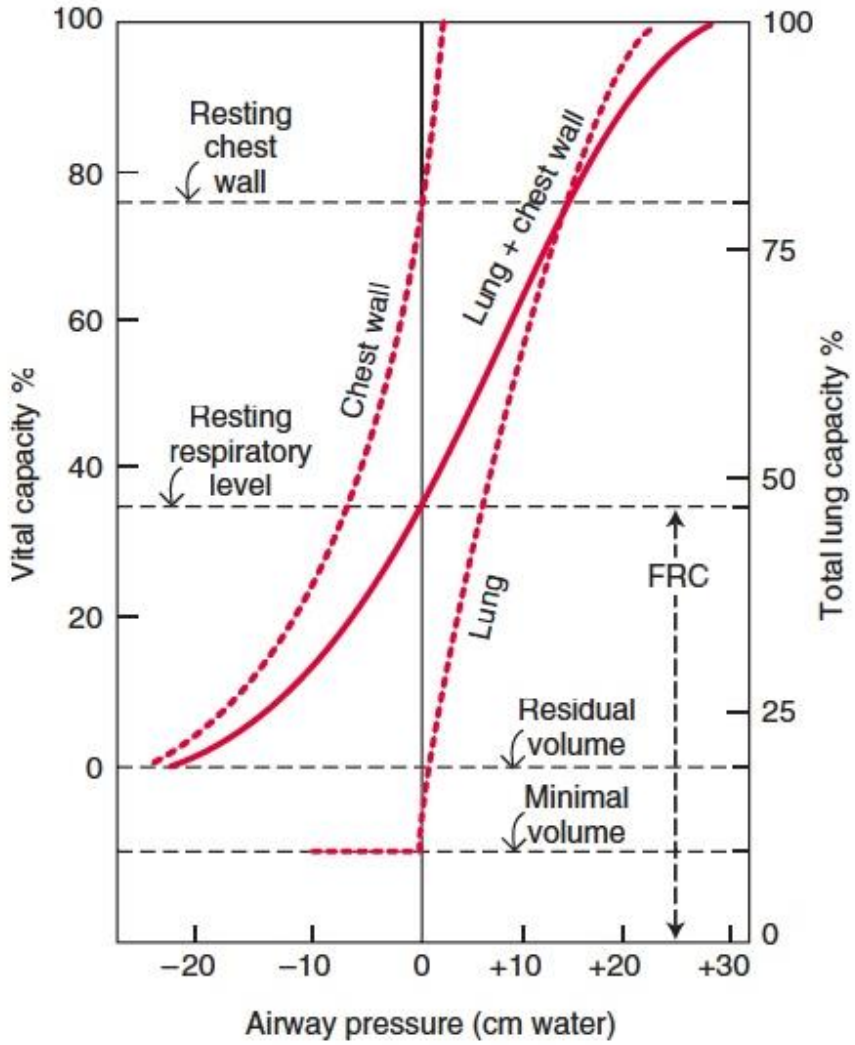

Figure 2-4: Pressure-volume diagram of the lungs, chest wall and total respiratory system

From Respiratory Physiology: The Essentials. 9th ed. 2012. West.[57]

Before the thorax can increase in volume, elastic recoil in the chest wall and lungs must be overcome. At FRC, total respiratory system elastance (E_{rs}) equals the sum of individual chest wall (E_{CW}) and lung elastance (E_L) (Equation 2). From this equation, it is apparent that C_{rs} is not simply the sum of C_L and C_{CW}.

$$E_{rs} = E_L + E_{CW}$$

$$\frac{1}{C_{rs}} = \frac{1}{C_L} + \frac{1}{C_{CW}}$$

Rearranging to determine C_{rs}: $$C_{rs} = C_{CW} \times \frac{C_L}{(C_{CW} + C_L)}$$

Equation 2: Elastance and compliance of the respiratory system

As illustrated in Figure 2-4, the slope of the pressure-volume or compliance curve of the lung is steepest and most linear at FRC. Below FRC, additional work is required to overcome surface tension forces within closed alveoli. Once recruited and partially opened, distension occurs more readily.[57] Near TLC, C_L decreases again as elastic recoil increases; lung fibres are stretched close to their distended limit, hence more pressure is required to produce additional change in volume. The chest wall also exhibits varied pressure-volume behaviour depending on where within the volume range it is measured. Together, these varying compliance characteristics give the pressure-volume curve of the respiratory system its sigmoidal shape, which becomes particularly relevant when the effect of NMD on lung volumes is considered (Section 2.4).

Lung compliance changes with age and overall size. Adult lungs are larger and accept more volume for any given pressure change than infant lungs, despite the inherent elastic properties of lung tissue being similar. Specific compliance, defined as C_L per unit of lung volume, expresses compliance as a function of actual volume (usually FRC), thereby standardising values:

$$Specific\ compliance = \frac{C_L}{FRC}$$

Equation 3: Specific compliance

With ageing, C_L at higher lung volumes decreases, but not at FRC or in the tidal breathing range.[71] However the reduction in C_{rs} associated with ageing is largely due to the chest wall, with C_{CW} decreasing independent of differences in size or height across the decades.[71,72] Age-related stiffening due to degenerative changes in vertebral joints and calcification of costal cartilages and chondrosternal junctions has been implicated.[72]

2.3.3.1 ASSESSMENT OF COMPLIANCE

A number of methods for assessing the different components of compliance exist (i.e., C_L, C_{CW}, C_{rs}, static and dynamic compliance), however these are typically invasive, require specialist equipment or considerable participant training. Static compliance is obtained during a period of zero flow, to eliminate the influence of airflow resistance, impedence and respiratory muscle effort. Measuring static C_L in spontaneously breathing participants requires an invasive technique that is technically difficult as respiratory muscles must be inactive during exhalation. An oesophageal balloon catheter is inserted to estimate P_{pl}. Participants inspire to TLC, and then passively exhale into a pneumotachometer. Exhalation is interrupted automatically by mouthpiece shutter occlusion, creating periods of no airflow. Transpulmonary pressure and lung volume recordings obtained at a minimum of six shutterpoints are used to construct a deflation pressure-volume curve of the lung, from which static C_L is calculated.[73,74] Whilst dynamic compliance is an easier technique to conduct, it provides different information to static C_L; dynamic C_L is obtained during periods of gas flow (i.e., active inspiration), and is therefore influenced by airway resistance, gas flow and respiratory muscle effort.

Measuring C_{rs} and C_{CW} is similarly challenging, historically requiring a closed-system body plethysmograph[75] or weighted spirometer.[76] A non-invasive technique for measuring C_{rs} exists (i.e., the "pulse method"[77]), however this is infrequently used in clinical practice. The pulse method is based on the principle that the volume and pressure change produced by a constant flow of air delivered to a closed receptacle (e.g., the respiratory system) over a known duration can be used to derive the compliance of that system. Participants breathe at tidal volumes through a sealed oro-

nasal mask, then passively relax whilst an inflation of air is delivered by an externally provided source at constant flow. The resultant volume delivered and corresponding pressure change are recorded and used to construct a pressure-volume curve, from which quasi-static compliance can be calculated.[77,78]

Seventy-five percent of participants in the study by Suratt *et al* could perform this technique, with values comparable to other methods of measuring C_{rs}. Additionally, C_{rs} values obtained within one sitting demonstrated adequate reproducibility, suggesting respiratory muscle relaxation occurred. Further work by the same group using this technique in ventilated patients demonstrated very similar pulse C_{rs} and static C_{rs} values within subjects (r=0.997).[79] The linearity of the pressure-time trace during the pulse inflation (scored on a scale between 1 and 10) correlated with diaphragm electromyogram activity,[80] suggesting that a linear pressure-time curve indicates relaxed respiratory muscles.

2.3.4 MECHANICS OF COUGH

Cough is the respiratory system's primary defence mechanism. It has roles in airway clearance, airway protection and lung protection, by i) removing sputum, mucus or foreign particles within the airway, ii) preventing or minimising aspiration of foreign material into the airway, and iii) protecting the lungs during a sudden external application of high distending pressure.[81]

Two neurophysiologically distinct cough pathways exist: a reflex or laryngeal cough, and a tracheobronchial cough. Both are executed via a complex reflex arc. The former is a vagally mediated reflex, activated when receptors situated in the larynx or proximal trachea are stimulated. These receptors respond primarily to mechanical stimuli, such as aspiration of foreign matter or excessive distension, and hence have a predominantly airway protection role. In contrast, tracheobronchial cough is generally associated with airway clearance. It can be reflex initiated by mucus or inhaled particles stimulating chemosensitive receptors distal to the larynx in the tracheobronchial mucosa and submucosa (a "spontaneous cough"), or voluntary (a "volitional cough").[82] Laryngeal and tracheobronchial coughs have different afferent inputs, neural pathways and efferent outputs.[83,84] In both cases, the motor response is complex, well-coordinated, involves activation of laryngeal, respiratory and abdominal muscles, plus reflexive activation of pelvic sphincters.[82]

A cough consists of three main phases: inspiratory, compressive and expiratory (Figure 2-5). A fourth "cessation" phase has also been described by some authors, referring to when the expiratory muscles relax and expiratory airflow becomes submaximal.[81,83] The inspiratory component consists of active abduction of the vocal cords (glottic opening) and inhalation of an adequate volume of air to forcibly exhale. At higher lung volumes, respiratory system elastic recoil increases, placing the expiratory muscles at an optimal length-tension relationship to generate the upcoming forced exhalation.

The size of this inspiration depends on the nature of the cough; during a reflex cough inspiration is minimal or absent, minimising the risk of foreign material penetrating

deeper into the airway.[81] Inspiration may range from 50% of V_T to 50% of VC during a tracheobronchial cough.[85] Other authors quote normal pre-cough inspiration of 85-90% of TLC.[86,87] Discrepancy between quoted inspiratory volumes likely reflects differences in muscle activity associated with effort, instructions or type of cough examined.[84,88]

During the compressive phase, the glottis closes and expiratory muscles contract to increase P_{pl} and hence intrathoracic pressure (time points 3 to 4 in Figure 2-5). This brief closure, lasting 200 milliseconds (ms), is performed by the adductor muscles of the arytenoid cartilages, reinforced by supraglottic structures including the ventricular folds and epiglottis.[81] Simultaneously, the expiratory muscles contract isometrically, raising intrathoracic and intra-abdominal pressures. The diaphragm activates in an antagonistic manner, to oppose the development of positive pleural pressure. In adults, intrathoracic pressures up to 300 mmHg (400 cmH_2O) have been described.[85] This closing and subsequent abrupt reopening of the glottis is a defining feature of a cough, separating it from a forced expiration. However, the actual significance of this on airway clearance is not clear; expectoration can occur in the absence of glottic closure, for example during a huff or forced expiration technique, or in people with a tracheostomy or laryngectomy.[81]

Sudden glottic opening by active abduction of the vocal cords marks the start of the expiratory phase. Pressure in the central airway (P_{AW}) falls abruptly to atmospheric, creating a pressure gradient between this point and the higher P_{pl} and P_A developed during the compressive phase. A 30 – 50 ms burst of supramaximal expiratory flow results, generating a transient "cough spike" with flow rates reaching 10-12 L/s (600-720 L/min).[81] Although expiratory flow falls following this cough spike to approximately 3-4 L/s (180-240 L/min), the cross-sectional area through which the gas is travelling also decreases meaning that airflow velocity remains high (due to dynamic airway collapse, explained further below). Expiratory flows continue for another 200-500 ms, with a concomitant drop in lung volume and P_{pl} (Figure 2-5).[85,89] The expiratory muscles remain active from the start of the compressive phase through to the completion of this expiratory phase.

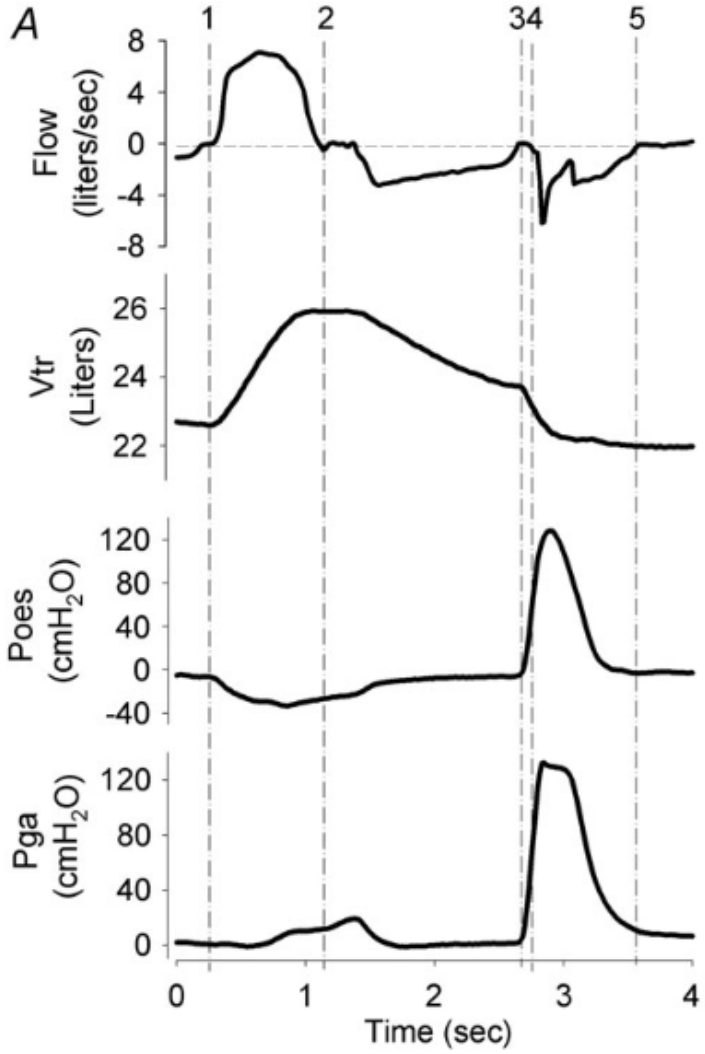

Figure 2-5: Cough mechanics: flow, volume and pressure signals during a voluntary tracheobronchial cough

Flow = flow at mouth, Volume = trunk volume measured via opto-electronic plethysmography, P_{oes} = oesophageal pressure (approximation of intrapleural pressure), P_{ga} = gastric pressure. Inspiratory phase = 1 to 2, Compressive phase = 3 to 4, Expiratory phase = 4 to 5. Note that in this illustration, time 2 to 3 signifies exhalation to a predetermined operating volume, as per the experimental protocol.

From Smith *et al*. Chest wall dynamics during voluntary and induced cough in healthy volunteers. 2012.[88]

High gas linear velocity (the distance travelled by gas molecules per unit time) is believed critical for removal of secretions from the periphery of the lungs to the larger central airways and mouth. Gas linear velocity is a function of flow and the cross-sectional area of the airways (Velocity = Flow / Area), therefore velocity can be enhanced by i) increasing expiratory flow, or ii) decreasing the cross-sectional area of the smaller airways. High intrathoracic pressure is necessary for both: airflow occurs from an area of high to low pressure, therefore an increase in P_{pl} and P_A during the inspiratory and compressive phases of cough will create i) a larger pressure gradient between the peripheral and proximal airways upon sudden glottic opening, promoting flow; and ii) a pressure gradient across the intrathoracic airways, whereby P_A is greater than P_{AW}. Modelling of this latter phenomenon is hypothesised to generate dynamic airway compression, resulting in a narrowing of airway calibre and subsequent increase in velocity for the same flow. This abrupt airway collapse is also postulated to cause airway wall vibration, higher kinetic energy and shearing forces, further enhancing mucus clearance.[90]

There is evidence that the volume of air displaced from the airways during cough increases as P_{pl} increases.[91] Moreover, it has been demonstrated that increasing expiratory flow does not enhance radio-labelled aerosol airway clearance; a volitional cough and huff both clear the airways, however the latter does so at lower peak expiratory flow rates.[92-95] Similarly, by placing a triggered shutter at the mouth, peak cough flow (PCF) rates can be generated above that of a volitional cough (564 ± 120 L/min *vs.* 246 ± 114 L/min), however clearance of radio-labelled aerosol remains the same.[95]

It has therefore been postulated that generating high intrathoracic pressure and causing dynamic airway compression may be more critical than flow for effective airway clearance, and that transient *supramaximal spikes* in flow (i.e., flow *greater than* that produced during a maximal forced expiration) signify this phenomenon.[91,96] "Cough spikes" are observed during huffs, reflex, spontaneous or volitional coughs, and are characterised by brief, rapid peak expiratory flows substantially higher than maximum, forced expiratory flow[91] (Figure 2-6). Cough P_{ga} is related to the presence or

absence of cough spikes,[96] implying that the generation of a cough spike may reflect cough mechanics better than the absolute PCF value reached.

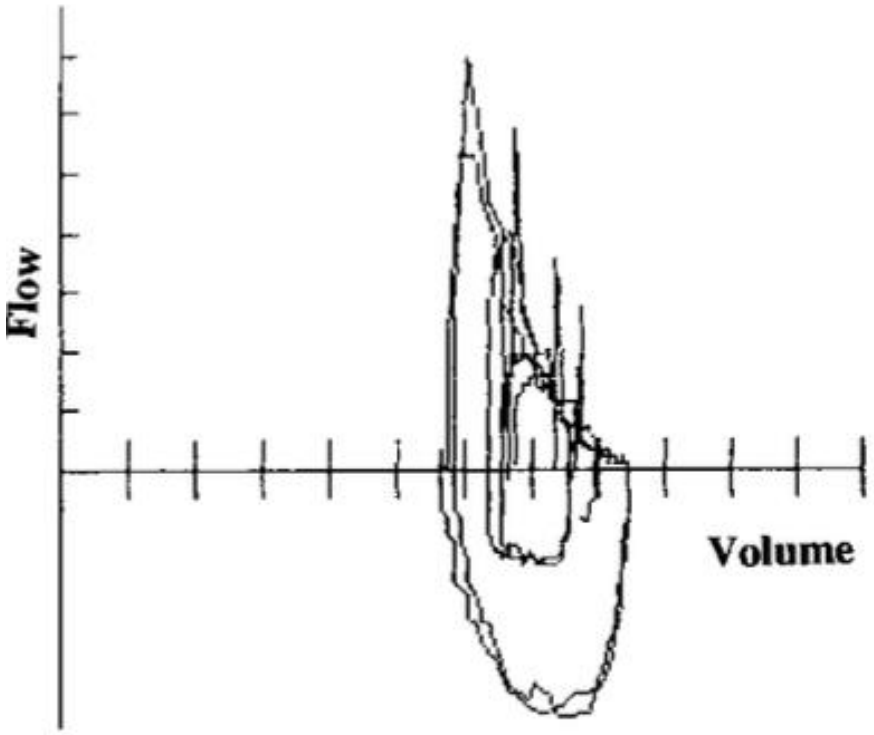

Figure 2-6: Flow-volume loop of a voluntary cough

Note that the flow-volume loop is superimposed on the maximal expiratory flow-volume curve (MEFV). The latter is obtained during a a maximal forced expiratory effort
From Polkey *et al.* Expiratory muscle function in amyotrophic lateral sclerosis. 1998.[96]

2.3.4.1 ASSESSMENT OF COUGH

Appreciation of cough neurophysiology and mechanics is growing, however the assessment of cough is not as well developed. The peak expiratory flow rate achieved during a cough (peak cough flow, PCF) is the most widely used measure and has been adopted as a surrogate marker of "cough effectiveness" particularly in NMD. Although PCF evolved from the measurement of peak expiratory flow (PEF), a forced expiratory manoeuvre easily and readily performed in non-laboratory settings to identify airflow

limitation,[97,98] PCF has not undergone the same scientific scrutiny. In contrast to assessment of lung volumes or respiratory muscle strength, assessment of cough is not well described. There is no procedure standardising equipment specifications such as device type, resistance and frequency response or preferred interface. Various equipment has been used, including analogue or digital peak flow meters,[99-106] handheld spirometers[107] and the gold-standard measurement device, a pneumotachometer;[108-112] yet inter-device agreement has not been adequately determined.

Peak flow meters, primarily used for PEF measurement in asthma management, are inexpensive, readily-available devices that have been repurposed by some clinicians and researchers to measure PCF. However considerable PEF measurement error has been demonstrated,[113-116] with one study reporting mean bias ranging from -47 to +17 L/min, depending on the brand tested (limits of agreement -139 to 109 L/min).[114] Moreover, a cough is likely to present even more of a challenge to measure as it has a shorter rise time compared to a forced expiratory manoeuvre.[117] Studies comparing PCF measured via pneumotachometer to peak flow meter values have produced conflicting results, with some authors suggesting they are comparable,[118,119] and others concluding the difference to be a significant source of measurement error,[120,121] or dependent on the measured range.[108]

Furthermore, clinical interpretation requires knowledge of "normal" values, within-subject repeatability and reproducibility, but these have not been satisfactorily established from adequately sized population studies using robust measurement methods. Studies have reported mean values for healthy participants that vary widely, likely attributable to small samples and/or the methods employed.[84,86,88,106,108,112,118,122-132] In one study that did endeavour to investigate repeatability of PCF using a pneumotachometer, individual coefficients of variation ranged from 8.7% to 20.3%. Based on within-subject repeatability over a four-week period, a single-reading was determined to be 76% reliable.[127] Other authors have likewise observed large intra-participant variability in NMD cohorts.[133]

Despite these issues, PCF is likely to be the most common cough measure in clinical practice. The latest European Respiratory Society statement on respiratory muscle testing includes PCF and states it "estimates the effectiveness of mucus clearance and expiratory muscle function".[134] Testing instructions, number of trials and acceptability of manoeuvre criteria are briefly described, although it should be noted that these are based on one existing study's method[108] rather than repeatability and reproducibility data.

2.4 RESPIRATORY DYSFUNCTION IN NEUROMUSCULAR DISEASE

Many of the studies investigating the physiological changes to respiratory function in people with NMD were conducted more than thirty years ago in small samples of people with spinal cord injury (SCI) or other long-standing and slowly-progressive NMDs. The aim was often to investigate the mechanics of normal respiration, taking advantage of the paralysis accompanying these NMDs to understand the role of respiratory muscles. More recently, observational cohort studies of patient populations have been published, providing information regarding the rate of decline associated with these conditions.

Restrictive ventilatory impairment is the hallmark of respiratory system involvement in people with NMD, with TLC, forced vital capacity (FVC) or slow VC declining as diseases progress. In people with DMD, there appears to be a linear decline in FVC between the ages of 11-22 years, of 4.5 to 5.0% predicted per year on average.[133,135-137] Treatment with glucocorticosteroid therapy preserves FVC %predicted for longer, however the rate of decline per year from peak FVC appears similar between steroid-treated and steroid-naïve patients.[138-140] Decline in MND is much faster, with loss of 3.1 to 3.5% predicted per month (37.2 to 42.0% predicted per year),[141,142] or an overall rate of -1.22 L/year prior to NIV implementation when all phenotypes are considered.[4]

Alteration in FRC is more variable than the fall in IC or VC. Some studies have demonstrated near-normal FRC values,[143,144] whereas others have reported a fall. A large study of 155 patients with NMD undergoing routine outpatient evaluation measured lung volumes in a study focusing on cough, and reported mean FRC % predicted of 69%, but over a very wide range (9 to 146%).[109]

Variations in distribution of muscle impairment are likely to explain the finding of differences in FRC; studies from people with SCI have demonstrated lower FRC in those participants with no intercostal activity compared to those with preserved intercostal function.[66,145] Similarly, FRC was more affected in participants with primary inspiratory muscle weakness[146] or when inspiratory muscle strength was lower,[147] suggesting both

diaphragm and intercostal muscle involvement. Given the role of the intercostal muscles in stabilising the ribcage, it follows that a loss of this muscle activity would produce less recoil force of the chest wall, meaning the equilibrium point between the lungs and chest wall would shift down (refer to Figure 2-4).

Whilst the prevailing view is that RV increases in NMD,[148] changes in RV are similarly dependent on the pattern of respiratory muscle weakness. People with expiratory muscle involvement demonstrate an increased RV and a reduced ERV, related to an inability to actively exhale below FRC.[66,146,149] Conversely in people with predominantly inspiratory muscle weakness, RV may be near normal or slightly reduced.[146,147,150] These studies all examined lung volumes in small samples (maximum of 27 participants) and did not include people with rapidly-progressive disease. Variability in these findings implies that lung volume change in people with NMD is not fully understood. Moreover, compartmental lung volume change has not been reported in people with MND.

In slowly-progressive NMDs, the reduction in lung volume and specifically VC reflects decline in IC and ERV related to inspiratory and expiratory muscle weakness.[135] However whilst VC is highly correlated with inspiratory muscle strength,[147] loss of lung volume is greater than that expected for the degree of muscle weakness.[66,143,147,151,152] In other words, weakness alone does not account for the degree of lung volume restriction seen. This seminal work conducted forty years ago hypothesised that respiratory system "stiffness" may play a role; reduced lung distensibility secondary to microatelectasis, and/or changes in the elastic properties of the lungs and chest wall may lead to a decrease in C_{rs}, thereby contributing to lung volume restriction.

There is some data to support this hypothesis. Five small studies have investigated C_{rs} (or have published raw C_L and C_{CW} values permitting calculation as per Equation 2) in people with NMD.[78,152-155] Although this measurement does not differentiate between lung and chest wall contributions it does reflect the respiratory system as a whole, and would suggest that C_{rs} is lower in this population compared to healthy control volunteers (Table 2-2). The overall loss in compliance has been postulated to be related to loss of volume secondary to alveolar collapse, alteration in lung tissue

and/or an inability to obtain full TLC due to muscle weakness or chest wall stiffness.[152,154] No data has been published examining C_{rs} in people with MND to date.

Author	Year	Number of participants	Population studied	Findings
Estenne[152]	1983	16 NMD 20 controls	Chronic SCI, slow NMD Healthy volunteers control	C_{rs} lower than controls (mean 0.078 *vs.* 0.135 L/cmH_2O) C_{rs} correlated with TLC and VC in both groups → Specific C_{rs} values similar. No correlation between C_{CW} and FRC
Estenne[153]	1986	20 NMD	Chronic SCI	Low C_{CW} and C_L compared to %predicted Calculated C_{rs} from raw data → mean 0.079 L/cmH_2O
McCool[154]	1986	14 NMD 6 controls	Slow NMD, chronic SCI Healthy volunteers control	C_{rs} lower than controls (mean 0.075 *vs.* 0.137 L/cmH_2O). C_{CW} and C_L lower than controls Specific C_{rs}, C_{CW} and C_L not different to controls
Scanlon[155]	1989	10 NMD 5 controls	Acute & chronic SCI Healthy volunteers control	Calculated C_{rs} from raw data → mean 0.105 *vs.* 0.158 L/cmH_2O C_L lower than controls but C_{CW} highly variable Specific C_{rs}, C_{CW} and C_L not different to controls
Molgat-Seon[78]	2017	12 NMD 12 controls	Slow NMD, chronic SCI Healthy volunteers control	C_{rs} lower than controls (mean 0.038 *vs.* 0.109 L/cmH_2O) No specific C_{rs} calculations possible

Table 2-2: Studies of respiratory system compliance measurements in NMD populations

NMD = neuromuscular disease, SCI = spinal cord injury, C_{rs} = respiratory system compliance, C_{CW} = chest wall compliance, C_L = lung compliance, TLC = total lung capacity, VC = vital capacity, FRC = functional residual capacity, Specific compliance = compliance divided by FRC.

A number of physiological studies, again conducted primarily in people with slowly-progressive NMD and with small sample sizes, have measured C_L with an oesophageal balloon catheter. These have all confirmed that people with long-standing NMD and weak respiratory muscles have reduced C_L (Table 2-3).[66,143,147,149,154-156]

One proposed mechanism is alveolar collapse. This could reduce C_L and lung volume in the affected areas, with the remaining, functioning alveoli retaining largely normal elastic properties, explaining the normal specific C_L observed by some authors.[66,147,154-156] However, a multifactorial mechanism is likely responsible, as the degree of atelectasis required to decrease volume and C_L has not been detectable on chest radiography or computed tomography scans.[66,143,149] A uniform increase in the surface tension of the alveolar lining layer due to breathing at low lung volumes,[157,158] or mechanical alterations in the elastic properties of lung tissue, caused by chronic shortening and stiffening of lung fibres due to their limited distension,[149,156] have also been postulated to reduce C_L.

Whether these changes apply earlier in disease onset or in rapidly-progressing disease to the same extent is unclear. In the only study examining C_L in patients with MND, lower C_L was observed in people with smaller lung volumes and more severe diaphragm weakness,[159] consistent with the findings above. However, only 14 participants were involved, some of whom had C_L values greater than the healthy volunteers. Whilst there was a statistically significant difference between people with MND and the control group (χ^2 p=0.044), there was no difference in specific C_L when this was calculated using data provided in the manuscript (χ^2 p=0.400), implying that the reduction in C_L may be a function of smaller lung volume. Likewise, in participants with other NMDs but mild respiratory impairment, the reduction in C_L observed was attributed to reduced lung inflation rather than lung parenchymal change.[160]

No data exists examining C_{CW} in people with MND, however people with long-standing NMDs do have lower C_{CW} compared to healthy participants.[152-154,161] Unlike C_L however, there appears to be no relationship between reduced C_{CW} and loss of FRC, leading authors to conclude that the reduction in end-expiratory lung volume is not an

important determinant of the loss of chest wall distensibility.[152,153] It has been proposed that breathing at small V_T and/or the absence of very deep breaths or sighs may lead to changes in ribcage motion over time. Stiffening or shortening of tendons, ligaments, costovertebral and costosternal articulations of the chest wall may contribute to the decrease in C_{CW} observed.[152,161]

Whilst decreased C_{CW} exists in the absence of gross musculoskeletal deformity or kyphocoliosis,[152,154] the presence of a kyphoscoliosis amplifies the reduction.[162] Pathology such as ribcage distortion and/or scoliosis is also likely to alter chest wall diameter and orientation of the ribcage, changing the mechanical forces produced by the respiratory muscles.[67,163,164]

One prospective cohort study of 39 paediatric patients with a NMD found that those with scoliosis had significantly lower FVC compared to children without a significant spinal curvature, despite reduction in maximal inspiratory and expiratory muscle strength in both groups. Participants with a scoliosis were older and had been living with disease for longer, implying that chronicity of condition may add a component of extra-thoracic restriction that further impairs respiratory function.[165] Retrospective longitudinal data from boys with DMD similarly suggests that increasing age and a greater thoracic angle of scoliosis independently predicted FVC.[135,166] Given the rapid onset of MND later in life when the spine and ribcage are fully developed, it is plausible that chest wall changes may be less prominent in this disease.

Regardless of the relative contributions of C_L and C_{CW} to the low C_{rs} seen in people with NMD, the result is that more energy has to be expended to overcome the recoil pressure of the lung and chest wall before inspiration can commence. Weak respiratory muscles, already at a force-generating disadvantage, must perform more "elastic work", meaning less resultant change in volume for the same pressure generated. Small samples in those with longstanding NMD provide overall support for the assertion that it is this loss of distensibility that is responsible for the disproportionate loss of lung volume, relative to muscle involvement,[66,143,147,149,151,152,154,156] however large studies are lacking. Importantly, no

data exists regarding how C_{rs} may change over time, or whether respiratory system stiffness is a significant factor in people living with MND.

Author	Year	Participant N°.	Population studied	Findings
Ferris[158]	1960	11 NMD 10 controls	Poliomyelitis Healthy volunteers control	C_L lower than controls
Gibson[143]	1977	7 NMD	Slow NMD	Low C_L - more than attributable to volume loss alone
De Troyer[147]	1980	25 NMD	Slow NMD	Low C_L correlated with TLC and VC, more than volume loss alone. Specific C_L normal
De Troyer[66]	1980	10 NMD	Chronic SCI	Low C_L correlated with TLC, more than volume loss alone. Specific C_L normal
De Troyer[156]	1981	10 NMD	Slow NMD	Low C_L correlated with TLC, more than volume loss alone. Specific C_L normal
Demedts[160]	1982	29 NMD	Slow NMD, minimal respiratory symptoms	Low C_L attributable to low volume
Estenne[152]	1983	16 NMD	Chronic SCI, slow NMD	C_L lower than %predicted (mean 0.170 L/cmH_2O, 69%pred)
Estenne[153]	1986	20 NMD	Chronic SCI	C_L lower than %predicted (mean 0.215 L/cmH_2O, 73%pred)
McCool[154]	1986	9 NMD 6 controls	Slow NMD, chronic SCI Healthy volunteers control	C_L lower than controls (mean 0.175 vs 0.253 L/cmH_2O) Specific C_L normal
Scanlon[155]	1989	10 NMD 5 controls	Acute & chronic SCI Healthy volunteers control	C_L lower than controls. Specific C_L normal
Estenne[149]	1993	14 NMD	Chronic SCI, slow NMD	Low CL but too much to be attributable to atelectasis alone.
Lechtzin[159]	2006	14 NMD 4 controls	MND Healthy volunteers control	C_L lower than controls (mean 0.164 vs 0.238 L/cmH_2O). Specific C_L similar (mean 0.033 vs 0.037 L/cmH_2O/L). Low C_L correlated with VC, more than volume loss alone

Table 2-3: Studies incorporating static lung compliance measurements in NMD populations
NMD = neuromuscular disease, SCI = spinal cord injury, C_L = lung compliance, TLC = total lung capacity, VC = vital capacity, Specific C_L = lung compliance divided by TLC.

2.4.1 COUGH IN PEOPLE WITH NEUROMUSCULAR DISEASE

Cough may be affected in people with NMD, due to inspiratory muscle weakness and/or reduced compliance restricting the inspiratory phase, uncoordinated or absent glottic closure during the compressive phase, and expiratory muscle weakness limiting the expiratory phase. As with other respiratory issues, the prevalence of an ineffective cough in people with NMD has not been clearly established.

Peak cough flow is the most widely used measure of cough in participants with NMD; of the 52 studies that have evaluated the effect of assisted inflation therapy during the manoeuvre, immediately following therapy or over time (Table 2-5, Table 2-6 and Table 2-7), 34 included PCF as an outcome measure. Lower PCF values have been reported in people with NMD compared to healthy control volunteers,[86,108,112,118,128,129] with one large population study observing a mean PCF value of 264 ± 108 L/min from 155 stable participants with NMD.[109]

The clinical significance of PCF is unclear; although PCF is commonly interpreted as a marker of cough effectiveness, few studies have related this to difficulty clearing secretions or expectorating sputum. Nonetheless, a threshold of 160 L/min has been reported as the PCF required for effective airway clearance,[13,53] based on the findings of Bach and Saporito.[103] This cohort study of adult patients managed at a single ventilator weaning unit aimed to explore parameters that predicted successful extubation or tracheostomy decannulation. They observed that 32 out of 37 participants achieved this outcome, all of whom recorded a PCF >160 L/min (with assistance).[103] However significant limitations of this study cast doubt on the validity of this cut-off, including the small single-centre sample, heterogeneous non-NMD diagnoses, omission of potential confounding factors on extubation success, poorly described statistical analyses, lack of an objective measure of “airway clearance” and no prospective validation.

Most studies concerning cough in people with NMD have not examined the ability of cough to clear secretions, instead focusing on the relationship between PCF and other

respiratory function tests. One of the largest studies tested 155 consecutive patients undergoing routine clinical review, and observed a correlation between PCF and VC (r^2=0.58). Stepwise regression identified that the IC component contributed 44% of the variance, with ERV and MEP also statistically significant (r^2=0.13 and 0.02 respectively).[109] Another large cohort of 179 stable participants with NMD, found that a VC >1.18 L or MEP >24 cmH_2O predicted the ability to achieve a PCF >180 L/min.[107] Other studies have similarly reported an association between measured PCF and VC, pre-cough inspired volume, maximal inspiratory pressure (MIP) and/or maximal expiratory pressure (MEP).[86,100,112,129,132,167-171]

Only a small body of research from Sancho and colleagues has defined cough functionally, by its ability to effectively clear secretions. A year-long prospective cohort study of participants with MND referred to a specialist centre evaluated PCF, peak velocity time, PCF/peak velocity time and other respiratory function measures. Forty patients subsequently had an episode of acute RTI, during which time 35% could clear secretions effectively; an "ineffective cough" was defined as one that was not able to remove respiratory secretions due to poor cough efforts, when associated with a feeling of retained secretions, abnormal breath sounds, dyspnoea and/or decreased oxyhaemoglobin saturation. Those who could not clear secretions during the RTI had lower FVC, MIP and MEP at baseline; PCF, PCF/peak velocity time and bulbar score most accurately predicted the patients who would proceed to having an ineffective cough when unwell (proposed PCF cut-off value <255 L/min).[111] The proportion of patients admitted for an acute RTI who could not clear secretions was higher in a subsequent study from the same centre; 44 of 48 participants had an ineffective cough with poorer FVC, PCF, MIP and MEP compared to the four patients who could cough effectively (proposed PCF cut-off value <166 L/min).[172] The same authors also looked at factors when medically stable that were associated with need for NIV during an acute RTI. Thirty-two patients who were not domiciliary NIV users were admitted over an 8-year period; 15 required NIV during the RTI episode and had lower FVC and PCF than those who were managed without ventilation (proposed PCF cut-off value <174 L/min).[173] These data imply an association between FVC, PCF and ability to clear

secretions, however all three studies omit characteristics of those patients who did not have a RTI from the analysis; whether they too had poor respiratory function but remained well and could effectively clear secretions is unknown.

Aside from PCF, the presence of transient supramaximal flow peaks has been used to evaluate cough (Figure 2-6). In a MND sample, the presence of cough spikes was associated with higher cough P_{ga}, however no relationship was observed between MEP and cough P_{ga}. Likewise there was no association between lower MEP and symptoms of poor cough.[96] These data are in contrast to other studies in MND and muscular dystrophy that found participants with cough spikes had higher MEP, MIP, PCF and VC compared to those without evidence of dynamic airway compression during cough. Considerable overlap of values was noted between the two groups, suggesting these markers may not discriminate between generation of cough spikes or not.[174,175] In people with MND, bulbar dysfunction was more prominent in those that could not generate a cough spike (72% compared to 17%),[174] supporting the findings of Sancho and colleagues that the glottis is an important contributor to an "effective cough".[111,173]

Collectively these studies imply that VC, MIP, MEP and/or bulbar function are associated with cough in people with NMD. Broadly, these measures reflect higher lung volume, diaphragm, abdominal muscle strength and better glottic closure, each important for generation of intrathoracic pressure. There are no data examining the correlation between these and P_{pl} in people with NMD, however based on first principles, it is likely that factors such as lung volume are linked to P_{pl} and hence an "effective cough" in this population.

It is postulated that the glottis assumes a larger role in cough when high P_{pl} cannot be generated via other means. A study conducted in participants with tetraplegia found that flow limitation and hence an effective cough can be achieved in the absence of expiratory muscle activity if vocal cord closure occurs. Whilst stimulation of the abdominal muscles during cough produced the highest P_{oes}, P_{ga} and PCF with concomitant airflow limitation in all, an un-stimulated cough (i.e., little or no expiratory muscle activity) against a closed glottis still achieved flow limitation in half

the group. An abdominal contraction with an open glottis produced the lowest P_{oes} and PCF values, resulting in flow limitation in 30% of cases.[176] These data imply that respiratory weakness and low PCF alone do not necessarily result in an ineffective cough, particularly if glottic function is intact.

These data demonstrate that people with respiratory muscle weakness can generate dynamic compression of intrathoracic airways, even at markedly subnormal peak P_{pl}.[177] Whilst the glottis is one determinant, people with lower C_{rs} can achieve an adequate P_{pl} due to the effect of higher chest wall and/or lung recoil pressures.[46] Thus people with NMD may not have normal cough mechanics, but may have a more effective cough than conventionally thought. This view has been shared by others, with Young and colleagues stating over 30 years ago: *"For almost 150 years the importance of high flow rates and glottic closure have dominated thinking on the mechanics of cough……It is equally important to consider that cough can be productive without glottic closure and with low flow rates".*[178]

2.5 IMPACT OF RESPIRATORY DYSFUNCTION IN NEUROMUSCULAR DISEASE

The above-mentioned physiological changes observed in people with NMD undoubtedly contribute to clinical outcomes. Decline in VC %predicted or markers of respiratory muscle strength indicate a struggling respiratory pump. As these values fall, oxygen desaturation during rapid-eye movement sleep[50], nocturnal[179] and daytime hypercapnia[180,181] become evident. Hypoventilation is one of the most significant respiratory issues in this population and faster rates of respiratory function decline are related to mortality. In a prospective cohort study of people with MND, the rate of decline in FVC %predicted was the single most important prognostic factor; patients who lost more than 3% predicted per month within the first six months after diagnosis were five times more likely to die compared to those with slower decline.[182] Markers of respiratory muscle strength likewise predict respiratory failure, time to NIV or mortality in MND.[181,183,184] Similar findings have been reported in other studies, whereby longer survival was associated with slower rates of deterioration in MND and DMD.[142,185]

Low lung volumes secondary to respiratory muscle weakness and stiffness may also predispose people to daytime hypoventilation. If FRC falls below the closing capacity of the lungs, alveoli are more prone to collapse, potentiating decline in C_L. Reduced lung volume, expiratory muscle weakness or bulbar dysfunction may also render cough ineffective. Many consensus statements or guidelines perceive people with NMD to have a greater risk of developing atelectasis, pneumonia or RTIs, and incorporate respiratory function cut-off values to guide the initiation of respiratory therapies.[10-12,15,53,54,186,187] Acute illness can exacerbate underlying respiratory muscle weakness, perpetuating respiratory dysfunction. Significant falls in MIP and MEP typically accompany viral upper RTIs in healthy adults and people with NMD, lasting up to 14 days post illness onset.[188,189] Shortness of breath, acute hypercapnia and decline in VC

were observed in a study of people with NMD, with the detrimental effects permanent in two of the 10 patients who developed a RTI.[189]

Respiratory complication rates in MND vary from 9% to 75% of participants.[105,111,190,191] Differences may be explained by study methodology (retrospective chart review versus prospective data), RTI definition used, observation period (12 to 50 months), sample source and selection bias (single versus multi-centre, jurisdictional model of health care) and respiratory care provided (multidisciplinary team access, NIV and respiratory adjuncts used). The large Canadian cohort by Rose and colleagues of all NMD diagnoses demonstrated a respiratory admission rate of 1.4 times every 3 years / person. Rates between diseases differed; people with MND were more than four times more likely to present to the emergency department than those with slowly-progressive NMD.[28]

There is similar imprecision in respiratory infection rate estimates in more slowly-progressive NMDs. A large retrospective survey of 672 ventilation users with NMD asked about prior episodes of pneumonia or hospitalization, however interpretation of this data is difficult as analysis was split into 18 treatment categories over different time periods, and overall rates were not well summarised.[192] Other retrospective studies from the same authors have compared episode and hospitalisation rates before and after introduction of a home-based respiratory monitoring protocol, however these data represent a biased sample of those patients with a history of RTI, limiting interpretation of respiratory complication rates in a broader NMD population.[193,194] The observation that none of the patients with a PCF >270 L/min developed an RTI, from one of these retrospective reviews of 48 patients,[194] has nonetheless been interpreted as the PCF threshold needed to prevent hospital admission and reduce the risk of pneumonia. This threshold features in many guidelines (along with PCF <160 L/min), with recommendations that assisted coughing strategies such as a mechanical insufflation-exsufflation (MI-E) be implemented once PCF <270 L/min.[12,13,15,53,54,186,187,195]

Other authors have also examined the frequency of RTI in their single-centre cohorts. Over half (59%) of a sample of 37 patients with DMD presenting for routine

assessment reported a RTI in the preceding year.[167] Using a similar conservative definition of "have you suffered a chest infection in the past year?", Dohna-Schwake and colleagues reported an average RTI rate of 0.84 ± 0.94 episodes/patient/year. Of the 46 paediatric participants with NMD, 22 patients (48%) reported a "severe chest infection" defined as an admission after the age of two, thereby including any episode within a 4 to 18 year period (participant mean age = 12.7 years). From these data, the authors proposed VC and PCF cut-off values that could distinguish those who had a severe RTI in the past or not (VC <1.1 L or PCF <160 L/min).[168] Similarly, retrospective chart review undertaken at a single SCI rehabilitation centre identified that 23% of patients over a four-year period had a diagnosis of pneumonia, with FVC and MIP being significantly lower in those who had.[196] In these retrospective studies, respiratory function was measured post RTI, hence poorer lung function may be a result of previous infection rather than a cause as has been implied. Prospective studies are required to determine risk of acquiring a RTI, however understanding characteristics associated with past history of RTI does inform this research.

2.6 RESPIRATORY MANAGEMENT IN NEUROMUSCULAR DISEASE

Given the relationship between poor lung function, morbidity and mortality, multidisciplinary respiratory care is vital for people with respiratory dysfunction secondary to NMD. Monitoring function, initiating therapies at the appropriate time, ongoing assessment and titration of treatments, responding to acute illness and providing suitable end-of-life care are all important clinical care objectives.

Ventilatory support is an established and key treatment for hypoventilation and chronic ventilatory failure; NIV has a significant impact on survival when nocturnal hypoventilation is present and is recommended in most clinical care guidelines.[13-16,187] A review of the effect of NIV is beyond the scope of this thesis, however many review articles have been published that synthesise the evidence.[5-9] A large cohort study from our centre observed a median survival of 28 months post symptom onset in people with MND treated with NIV, compared to 15 months in those who were not.[4] This survival advantage of 13 months in the NIV-treated group is substantially more than the 2-3 months survival benefit attributable to riluzole,[197] the only drug approved for treatment of MND in Australia.

Adjunctive respiratory management of people with NMD is less clearly defined. Summarising the evidence of efficacy is challenging as the research is of a lesser quality, and various techniques and dosages employed.[18] Whilst there is a small body of research investigating inspiratory and/or expiratory respiratory muscle training in this population,[198-204] most clinical and research activity is focussed on airway clearance techniques (ACT).

Airway clearance techniques are therapies that aim to improve cough effectiveness, mobilise mucus and increase lung volume (Table 2-4). A consensus meeting convened in 2017 by the European Neuromuscular Centre discussed the “clearance” function of ACTs, categorising techniques as peripheral ACTs (techniques that improve ventilation, loosen secretions and enhance mucus transport from peripheral to central airways), or proximal ACTs (techniques that augment cough). The authors concluded that ACTs are

beneficial for mucus clearance and cough augmentation, however the effect of ACTs on lung volume was not discussed in detail.[10,11] A narrative review extended this work by considering the volume augmentation effects of these techniques.[18]

Airway clearance techniques have traditionally been employed to augment cough or to reinflate areas of collapsed lung, improve alveolar ventilation, mobilise mucus from the peripheral and central airways during sputum encumbrance or acute respiratory illness.[205] However, more recently it has also been recommended that they be performed routinely.[12-17] This shift, from initiating treatments only when there is a clear indication to a proactive approach of introducing therapies earlier, has occurred in parallel with advances in the medical management and prognosis of many NMDs.[14,206] Many patients are living longer with a chronic disease, with therapy aims reflecting this chronic disease management paradigm.

"Assisted inflation" ACTs increase inspiratory volume above the spontaneous unassisted IC, thereby hyperinflating the lungs and mobilising the chest wall. Volume recruitment techniques (namely manual hyperinflation or ventilator hyperinflation[205,207]) do increase lung volume, sputum clearance and C_{rs} in intubated and ventilated patients.[19-21] Multiple authors have speculated that augmenting lung volume in people with respiratory muscle weakness or restrictive chest wall disease when well may improve respiratory system "flexibility" and prevent deleterious respiratory sequelae.[14,15,53,136,208] Averting RTIs, particularly in patients with a history of recurrent episodes, may prevent secondary parenchymal pathology or further lung function decline. Extrapolating from data in NIV, it has also been postulated that slowing lung volume decline may have a beneficial effect on respiratory symptoms, complications and potentially even survival.

Whilst there is clinical rationale and biological plausibility to hypothesise that assisted inflation therapies may maintain or improve lung volumes, C_{rs} and potentially slow the decline in respiratory function, there is a paucity of research to support this view. Additionally, the burden of performing regular treatment and the impact on quality of life (QoL) has not been established.

Given the lack of compelling evidence but the potential for routine respiratory therapy to maintain or slow the decline in respiratory function in people with progressive NMD, there is a strong need for prospective, controlled research. Lung volume recruitment (LVR) is one method of assisting inflation that has wide clinical appeal. It is a simple therapy that uses inexpensive and widely-available equipment, thereby having advantages over other assisted inflation techniques that require a machine to deliver driving pressure. This therapy and the current evidence-base for LVR are detailed below.

Objective	Method	Technique	Type
Cough augmentation	Inspiratory assistance	Single or Stacked breath methods	Assisted inflation therapies (see below)
	Expiratory assistance	Manual	Manually assisted cough (MAC)
		Mechanical	ME of MI-E
	Combined assistance	Manual	Inflation + MAC
		Mechanical	Mechanical insufflation-exsufflation device (MI-E)
Volume augmentation	Assisted inflation	Stacked-breath methods	Glossopharyngeal breathing
			LVR: manual resuscitation bag
			LVR: VCV-NIV
		Single-breath methods	Pressure-limited NIV
			Inspiratory positive pressure breathing device (IPPB)
			MI of MI-E
Sputum clearance	Peripheral ACT / Sputum mobilising	Manual	Manual techniques (positioning, percussion, vibrations)
			Chest wall strapping
		Mechanical	Intrapulmonary percussive ventilation
			High frequency chest wall oscillation
	Proximal ACT / Cough augmentation	Inspiratory, Expiratory or Combined methods	See above

Table 2-4: Taxonomy for airway clearance techniques

MAC = manually assisted cough, ME = mechanical exsufflation, MI-E = mechanical insufflation-exsufflation, LVR = lung volume recruitment, NIV = non-invasive ventilation, VCV-NIV = volume-limited mode (i.e., volume-controlled ventilation) of non-invasive ventilation, IPPB = inspiratory positive pressure breathing, MI = mechanical insufflation.

2.7 LUNG VOLUME RECRUITMENT

Lung volume recruitment, commonly known as 'breath-stacking', is a stacked-breath assisted inflation technique, achieved using a manual resuscitation bag or volume-limited mode (i.e., volume-controlled ventilation) of NIV (Table 2-4). Regardless of the source of driving pressure, a number of consecutive compressions or insufflations are performed, without exhaling in between, creating a "stepped" pattern of inspiration, until the maximum, tolerable inflation capacity is reached. This volume, equivalent to an externally-assisted IC, is termed the maximum or lung insufflation capacity (MIC or LIC), depending on whether glottic control is necessary for the assisted inflation (MIC) or not (LIC).[10,209] When employed for cough augmentation, exhalation from MIC or LIC is forced (i.e., cough or huff) and may be combined with expiratory assistance such as a manually assisted cough (MAC). In contrast, if the primary aim is volume recruitment, assisted inflations are followed by passive exhalation to FRC.

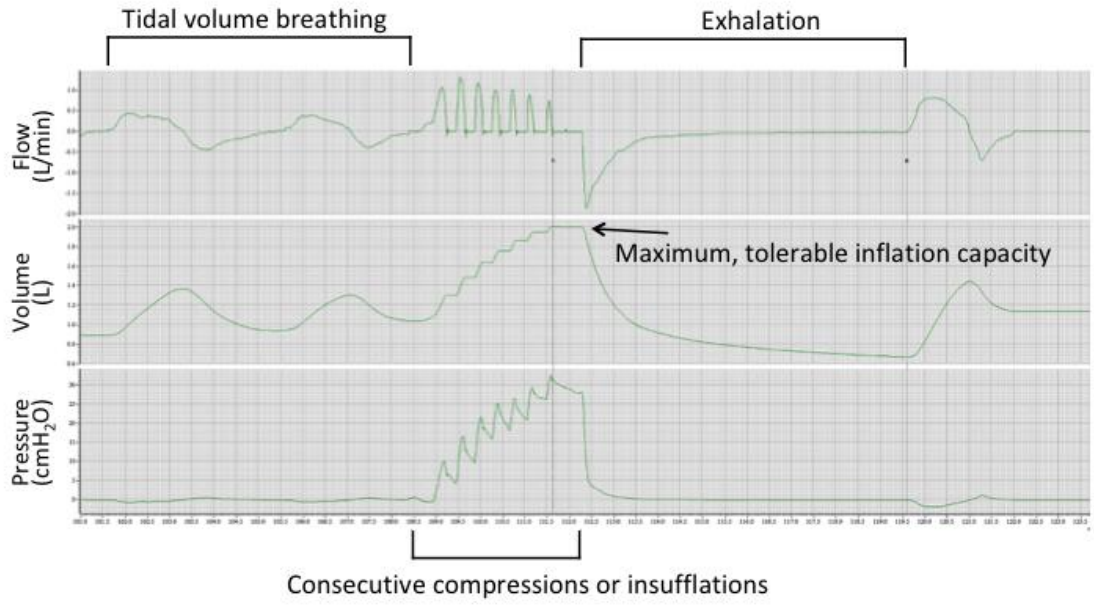

Figure 2-7: Flow, volume and mouth pressure traces of tidal breathing followed by a single repetition of lung volume recruitment.

Horizontal axis represents time (500 msec intervals).

The “stacking” of breaths distinguishes LVR from other methods of assisted inflation. Stacked-breath methods are characterised by brief plateaus of zero flow between consecutive insufflations, whereas single-breath methods reach LIC with a single insufflation. All methods can be delivered via a mouthpiece or oro-nasal mask. If the latter is used, intact bulbar function is theoretically not required for single-breath methods, as the devices can be set to deliver a volume that exceeds unassisted spontaneous IC. However, glottic control is necessary to perform glossopharyngeal breathing, LVR with a volume-limited NIV machine, or LVR with a manual resuscitation bag without a one-way valve, as the vocal cords must repeatedly abduct whilst insufflating then adduct to hold the insufflated volume until MIC is reached. Commercially-available LVR kits contain a one-way valve (or one can be placed in line with a resuscitation bag) thereby avoiding the need for adequate bulbar function. If this equipment is employed, the term LIC should be applied.

An advantage of LVR over other methods is its availability. Equipment is lightweight, portable, inexpensive (approximately $32 AUD) and comes ready-assembled in commercial LVR kits. Alternatively, a standard manual resuscitation bag found in any hospital can be employed. Single-breath methods of inflation require a machine to deliver the driving pressure; if patients are not using NIV at home then this incurs an additional cost to the individual or health care system. If the person is an existing NIV-user, their ventilator could be utilised, but not all machines are capable of performing volume-limited ventilation. Pressure-limited bilevel devices such as a VPAP™ or BiPAP™ machines are the most commonly prescribed domiciliary NIV machines and can be used, however this usually requires changing ventilator settings from nocturnally prescribed pressures to assisted inflation settings for each therapy session, introducing a potential source of human error. Inspiratory positive pressure breathing (IPPB) devices or MI-E machines avoid this risk, as they are used for the single purpose of hyperinflating and are fully programmable, however they are expensive (approximately $10,000 AUD), heavier and less portable. Whilst these machines may be available or funded in some jurisdictions, their cost is prohibitive in many other environments. Furthermore, they arguably require more specialised skills to

titrate[210,211] and set-up initially, and may require ongoing technical support and service; additional barriers to access.

In addition to equipment used or role of the glottis, there are other minor differences in how assisted inflation therapies are applied clinically, although research evaluating these variations is limited. No research has been conducted examining the effect of starting volume on MIC or LIC, although variation is reported; some studies commence insufflations *after* an active breath to spontaneous IC,[101,170,208,212,213] whereas other researchers either start at FRC or have not defined the starting volume.[102,105,107,136,137,209,214-220] A single study reported larger volumes obtained when participants actively inhaled and exhaled with a MI-E device compared to passively accepting the pressures delivered, however this is the only research thus far to have investigated this.[221] These practice variations may be necessary to optimise titration of the therapy to each individual, and differences in efficacy between techniques at a group level are unlikely.

2.7.1 Effect of LVR on Volume and PCF during the Manoeuvre

The aim of assisted inflation techniques is to hyperinflate the lungs to a maximum, safe, tolerable, volume that is higher than the person's own spontaneous IC. Broadly, assisted inflation therapy has consistently demonstrated that a LIC or MIC greater than VC can be obtained in almost all of the selected participants, and that a cough initiated from this augmented volume can increase the measured PCF (Table 2-5). However, when comparing different assisted inflation techniques, the vast majority of studies have focused on PCF rather than quantifying the increase in volume achieved or the physiological effects of a single therapy session.

Studies evaluating the effect on volume would indicate that no one method of hyperinflation is superior overall. The proportion of participants with DMD who could successfully employ LVR using a resuscitation bag was similar to the success rate using volume-limited NIV to stack (88% *vs.* 89%).[222] No difference was found between-groups in the MIC achieved (bag = 1344 ± 520 mL *vs.* NIV = 1481 ± 477 mL, p=0.33), or

the PCF obtained when coughing from the inflated volume (bag = 186 ± 50 L/min *vs.* NIV = 199 ± 48 L/min, p=0.33).[222] Similarly, the MICs obtained using IPPB or a MI-E device for inflation,[223] or with stacked- and single-breath methods appear comparable.[224] In the latter study, seven participants could achieve higher inflation volumes with the stacked-breath technique, whereas the single-breath method was superior in 11 (two participants obtained equivalent volumes).[224] These findings suggest that different methods of assisting inflation can provide similar improvements in volume, and individualised assessment is important to determine the technique most beneficial for each patient.

In contrast, one case series of 282 consecutive patients attending a single centre reported that LVR using a bag and one-way valve resulted in a larger assisted inflation than LVR via volume-limited NIV or a bag without a valve, although both methods achieved assisted ICs above spontaneous VC (LIC = 2069 ± 867 mL (range 320 – 5400) *vs.* MIC = 1712 ± 926 mL (range 30 – 5100) *vs.* VC = 1131 ± 744 mL (range 0 – 3580)).[209] This retrospective data did not report the prevalence of bulbar dysfunction, and it is not known whether the order of assessment was randomised; if LVR has a short-term physiological effect on respiratory function this may influence subsequent values. Discord in the magnitude of volume augmentation with different LVR techniques between this large retrospective study and smaller prospective studies reported in Table 2-5 may represent individual participant or clinician technique, further highlighting the need for individualised assessment and titration.

Numerous studies have also evaluated the ability of LVR and other assisted inflation techniques to augment cough in people with NMD during periods of stability. Notwithstanding the previously detailed limitations of PCF as an outcome measure (Section 2.3.4.1), the PCF when coughing from an inflated volume is larger than an unassisted volitional cough (Table 2-5). Furthermore, a positive association exists between the amount of volume recruited (MIC – VC difference) and the increase in augmented PCF ($PCF_{assisted}$ – PCF difference).[170,212,224,225] One study has found this relationship extends to an optimal inflation capacity, with $PCF_{assisted}$ declining past this

point.[99] The clinical significance of generating a larger PCF has not been definitively established.

Author/s	Year	Number of participants	Population	Trial design	Hyperinflation therapy	Results	Comparison b/w methods*
Bach[102]	1993	21	Slow NMD	Prospective	LVR with VCV-NIV MI-E	MIC > VC $PCF_{MI-E} > PCF_{MIC+MAC} > PCF_{MIC} > PCF$	PCF
Kang[170]	2000	108	MND Slow NMD	Case series	LVR with bag *or* LVR with VCV-NIV	90/108 patients: MIC > VC $PCF_{MIC+MAC} > PCF$	None
Sivasothy[128]	2001	12	Slow NMD	Prospective Randomised order	MAC MI with MI-E MI + MAC	IC not measured $PCF_{MI+MAC} = PCF_{MAC} > PCF_{MI} = PCF$	PCF
Chatwin[112]	2003	22	Slow NMD	Prospective Randomised order	MAC NIV ME of MI-E MI-E	IC not measured $PCF_{ME} = PCF_{MI-E} > PCF$	PCF
Mustfa[129]	2003	47	MND	Prospective Randomised order	MAC ME of MI-E MI of MI-E MI-E	IC not measured $PCF_{MAC} = PCF_{ME} = PCF_{MI-E} > PCF$	PCF
Sancho[215]	2004	26	MND	Prospective	LVR + MAC MI-E + MAC	24/26 patients: MIC > VC	PCF
Kang[212]	2005	71	DMD	Prospective	LVR MAC LVR + MAC	MIC > VC $PCF_{MIC+MAC} > PCF_{MAC} = PCF_{MIC} > PCF$	PCF
Trebbia[109]	2005	10	Slow NMD	Prospective Randomised order	MAC IPPB IPPB + MAC	LIC with IPPB+MAC > IPPB alone $PCF_{IPPB + MAC} > PCF_{IPPB} = PCF_{MAC} > PCF$	IPPB *vs.* IPPB + MAC PCF

Author/s	Year	Number of participants	Population	Trial design	Hyperinflation therapy	Results	Comparison b/w methods*
Dohna-Schwake[225]	2006	29	NMD	Prospective	IPPB	28/29 patients: LIC > VC 27/29 patients: $PCF_{IPPB+MAC}$ > PCF	None
Kang[171]	2006	40	SCI	Prospective	LVR MAC LVR + MAC	MIC > VC $PCF_{MIC+MAC}$ > PCF_{MAC} > PCF_{MIC} > PCF	PCF
Bach[216]	2007	78	DMD	Case series	LVR with bag *or* LVR with VCV-NIV	74/78 patients: MIC > VC $PCF_{MIC+MAC}$ > PCF	PCF
Bach[209]	2008	282	MND Slow NMD	Case series	LVR with bag *or* LVR with VCV-NIV LVR with bag & valve	LIC > MIC > VC PCF_{MIC} > PCF. Did not measure PCF_{LIC}	LIC *vs.* MIC
Ishikawa[218]	2008	61	DMD	Prospective Randomised order	LVR MAC LVR + MAC	IC not measured $PCF_{LVR+MAC}$ > PCF_{LVR} > PCF_{MAC} > PCF	PCF
Toussaint[107]	2009	179	Slow NMD	Prospective	MAC LVR with VCV-NIV LVR + MAC	IC not measured $PCF_{LVR + MAC}$ > PCF_{LVR} = PCF_{MAC} > PCF	PCF
Brito[169]	2009	28	DMD	Prospective Randomised order	MAC LVR LVR + MAC	IC not measured $PCF_{LVR + MAC}$ > PCF_{LVR} = PCF_{MAC} > PCF	PCF
Senent[110]	2011	16	MND	Prospective Randomised order	MAC LVR + MAC NIV + MAC MI-E	IC not measured $PCF_{LVR+MAC}$ = $PCF_{NIV+MAC}$ = PCF_{MI-E} > PCF_{MAC} > PCF	PCF

Author/s	Year	Number of participants	Population	Trial design	Hyperinflation therapy	Results	Comparison b/w methods*
Lacombe[223]	2014	18	Slow NMD	Prospective Randomised order	IPPB + MAC MI-E MI-E + MAC	LIC achieved with all three conditions greater than unassisted $PCF_{IPPB + MAC} > PCF_{MI-E + MAC} > PCF_{MI-E} >$ PCF	Single-breath: IPPB vs MI PCF
Mellies[99]	2014	29	Slow NMD	Prospective Randomised to group	IPPB Lung insufflation assist manoeuvre (LIAM)[1]	$LIC_{IPPB} > VC$, and $LIC_{LIAM} > VC$ Optimal LIC to achieve highest assisted PCF = 89-91% of max LIC	Between group comparison not made
Torres-Castro[101]	2014	15	SCI	Prospective Randomised order	MAC LVR LVR + MAC	IC not measured $PCF_{LVR + MAC} > PCF_{LVR} = PCF_{MAC} >$ PCF	PCF
Toussaint[222]	2016	52	DMD	Prospective Randomised to group	LVR with bag LVR with VCV-NIV	$MIC_{bag} = MIC_{VCV-NIV}$ $PCF_{bag} = PCF_{VCV-NIV}$	Bag *vs.* VCV-NIV PCF
Santos[221]	2017	47	Slow NMD	Prospective	Passive MI-E Actively assisted MI-E	$LIC_{active} > LIC_{passive} >$ Spontaneous IC	MI-E with passive or active assistance
Nygren-Bonnier[226]	2018	10	SCI	Prospective	Glossopharyngeal breathing	MIC > VC. Also increased TLC, HR during manoeuvre, decreased MAP	N/A: Physiology study
Del Amo Castrillo[224]	2019	20	Slow NMD	Prospective Randomised order	LVR with VCV-NIV (MIC) Volumetric cough mode (VCM)[2] (LIC)	MIC *vs.* LIC not statistically different $PCF_{LIC} > PCF_{MIC} >$ PCF Comfort and perceived cough effectiveness similar	VCV-NIV *vs.* VCM PCF

Table 2-5: Studies examining Assisted Inflation, in medically-stable participants with NMD

Comparison between methods* does not include comparison with baseline or control (i.e., unassisted PCF vs assisted PCF).
Shaded rows highlight studies that compared degree of inflation volume between techniques.
NMD = neuromuscular disease, MND = motor neurone disease, DMD = Duchenne muscular dystrophy, SCI = spinal cord injury.
LVR = lung volume recruitment, VCV-NIV = volume-limited non-invasive ventilation, MI-E = mechanical insufflation-exsufflation, MAC = manually assisted cough, MI = mechanical insufflation, NIV = non-invasive ventilation, ME = mechanical exsufflation, IPPB = inspiratory positive pressure breathing.
[1] VENTIlogic LS ventilator mode: pressure-controlled manoeuvre with preset insufflation time and pressure plateau phase
[2]Astral 150 (Resmed) ventilator mode: volume-controlled hyperinflation breath titrated to achieve LIC, with maximum allowed 500% of baseline V_T or PIP 50 cmH_2O
MIC = maximal insufflation capacity, VC = vital capacity, PCF = peak cough flow, LIC = lung insufflation capacity, IC = inspiratory capacity, TLC = total lung capacity, HR = heart rate, MAP = mean arterial blood pressure.

2.7.2 IMMEDIATE EFFECT OF LVR DURING PERIODS OF STABILITY

Whilst LVR can augment volume[78,136,137,170,209,213,215,220,222] and increase the PCF produced *during* the manoeuvre,[101,102,107,110,169,170,209,212,215,218,222,227] the effects of a single session of therapy are less well established. Of the studies that have investigated the immediate effects of a single-session of assisted inflation on respiratory function (Table 2-6), only two small studies have examined the efficacy of LVR in people with NMD,[78,219] whilst a third studied healthy participants.[228]

Improvements in volume and cough flow whilst performing LVR (i.e., MIC and PCF_{MIC}) have been shown in 20 healthy participants using opto-electronic plethysmography. The increase in chest wall displacement was largely attributable to the pulmonary ribcage compartment, with a concomitant reduction in abdominal compartment contribution. Following three maximal inflations, volume and breathing pattern returned to pre-LVR values, indicating no carry-over or immediate effects of a single-session in this healthy population.[228]

Author/s	Year	Number of participants	Population	Trial design	Hyperinflation therapy	Results
Sinha[229]	1972	6	Restrictive CWD	Prospective pre-post intervention study	5 minutes IPPB	Dynamic C_L increased immediately post; sustained 1 hour. Elastic WOB decreased
De Troyer[156]	1981	10	Slow NMD	Prospective pre-post intervention study	15 minutes IPPB (also performed maximal inflations using VCV-NIV in sub-set)	No change in VC, FRC, C_L,
McCool[154]	1986	14 NMD 6 Controls	Chronic SCI, slow NMD	Prospective pre-post intervention study	20 minutes IPPB	No change in C_{rs} (or C_L and C_{CW} in sub-set with measurements)
Simonds[230]	1989	10	Restrictive CWD		5 minutes MI (volume or pressure NIV)	No change in accessible alveolar volume or oxygenation
Stiller[231]	1992	5	Recent SCI		20 minutes IPPB (4 reps x 6 sets)	Statistically significant but small change in VC post therapy (0.4 ± 0.9 L)
Lechtzin[159]	2006	14 MND 4 Controls	MND	Prospective pre-post intervention study	5 minutes MI (bilevel NIV)	No group change in C_L.
Laffont[232]	2008	7	Recent SCI	Prospective pre-post intervention study	20 minutes IPPB	No change in dynamic C_L or WOB post
Guerin[233]	2010	14	Slow NMD	Prospective pre-post intervention study	30 maximal inflations via IPPB	Improved tidal volume (V_T) on EIT, up to 3 hours post single-session

Author/s	Year	Number of participants	Population	Trial design	Hyperinflation therapy	Results
Cleary[219]	2012	26 PCF data 15 FVC data	MND	Prospective, pre-post cross-over study	5 maximal inflations via LVR	Improved PCF post, no change in FVC
Meric[234]	2016	9	DMD	Prospective pre-post intervention study	15 maximal insufflations via MI-E	Statistically significant increase in VC post therapy, but small magnitude & diminished by 1 hour. No change in V_T
Molgat-Seon[78]	2017	12 NMD 12 Controls	Slow NMD, Chronic SCI	Prospective pre-post intervention study	10 maximal inflations via LVR	Immediate increase in C_{rs} – diminished by 1 hour. No change in VC, FRC, PCF.
Cesareo[235]	2018	20	DMD	Prospective pre-post intervention study	5 x 5 maximal insufflations via MI-E (for lung volume recruitment)	No change in VC, V_T or PCF post MI-E. No change in lung volumes via OEP

Table 2-6: Studies investigating the immediate effect of Assisted Inflation in participants with NMD

Shaded rows highlight studies employing LVR.

CWD = chest wall disease, NMD = neuromuscular disease, SCI = spinal cord injury, MND = motor neurone disease, DMD = Duchenne muscular dystrophy.

IPPB = inspiratory positive pressure breathing, VCV-NIV = volume-limited mode (i.e., volume-controlled ventilation) of non-invasive ventilation, MI = mechanical insufflation, NIV = non-invasive ventilation, LVR = lung volume recruitment, MI-E = mechanical insufflation-exsufflation.

C_L = lung compliance, WOB = work of breathing, VC = vital capacity, FRC = functional residual capacity, C_{rs} = respiratory system compliance, C_{CW} = chest wall compliance, V_T = tidal volume, EIT = electrical impedence tomography, FVC = forced vital capacity, PCF = peak cough flow, OEP = opto-electronic plethysmography.

Cleary and colleagues conducted a cross-over trial, comparing a single-session of LVR (5 maximal inflations and 2 assisted cough manoeuvres) to a control period in 29 participants with MND who used LVR at home. Forced vital capacity, PCF and sniff nasal inspiratory pressure (SNIP) were measured at baseline, 15 and 30 minutes post therapy. A significant interaction effect was found, however this represented a statistically significant difference in FVC between groups at 15-minutes only. No change in FVC over time was found in the LVR or control arms; a small improvement of 70 mL was noted (mean change of 3%) but this was not clinically or statistically significant. Unassisted PCF increased post-LVR at 15 and 30 minutes after the single-session compared to baseline, with significant between-group differences. The authors postulated that the mean increase of 54 L/min may represent an improvement in compliance, however given the lack of concomitant increase in lung volume and that C_{rs} was not assessed, this change may also reflect PCF measurement variability.[219]

In contrast, C_{rs} was a novel outcome that was measured in a pre-post intervention study conducted in 12 participants with slowly-progressive NMDs and 12 healthy control participants.[78] Lung volume recruitment comprised ten maximal inflations, resulting in a significant increase in volume (MIC) and PEF_{LVR} at the time of therapy in participants with NMD, the latter likely due to an increase in elastic recoil at the higher volume. Between-group differences were observed at all time points, with PCF and all lung volumes except RV significantly lower in the NMD cohort. However, in contrast to the study in people with MND, neither group demonstrated an effect of LVR on unassisted PCF or lung volumes over time.[78]

Respiratory system compliance, measured using the pulse inflation method,[77] was lower in the NMD group relative to controls. Immediately following a single-session of LVR, there was an improvement in C_{rs} (37 ± 5 to 50 ± 7 mL/cmH_2O) representing a change of 40 ± 10%, however levels had returned to baseline within an hour. Individual data suggests there may be responders and non-responders; 8 out of 12 participants obtained an improvement greater than 20% of baseline, whereas the other third had smaller or a negative response. Another interpretation may be that the findings represent test/re-test variability. The authors concluded that resolution of atelectasis

was not the mechanism by which C_{rs} increased, as static lung volume did not change, but further research is required to elucidate the mechanism and determine whether regular LVR is associated with prolonged improvements in respiratory mechanics.[78]

The remaining research employing alternative methods of assisted inflation, do not demonstrate conclusive findings (Table 2-6). Whilst some studies suggest an improvement in C_L and/or lung volume following a single-session of therapy, others found no change in these parameters. Given the small number of participants involved (ranging from 6 to 20) this lack of consensus is not surprising; it is plausible that there are responders and non-responders, perhaps related to individual baseline characteristics such as degree of lung volume restriction. Alternatively this variation may be random and reflect no true effect. Moreover, aside from the research by De Troyer[156] and Molgat-Seon,[78] comprehensive evaluation of respiratory mechanics incorporating lung volumes and compliance measures has not been conducted in participants with NMD.

2.7.3 EFFECT OF REGULAR LVR THERAPY

Research evaluating the regular use of assisted inflation therapy is largely retrospective or uncontrolled in design (Table 2-7), but nonetheless has contributed to recommendations that daily LVR therapy be performed routinely by people with NMD.[12,14-17] There have been two RCTs, two prospective uncontrolled trials, and seven retrospective case series or cohort studies examining LVR. The latter study designs are limited by the absence of a control or comparator cohort to account for the natural history of respiratory function decline in progressive NMDs, and the use of self-report to determine performance of daily therapy, which in other areas has been shown to be unreliable.[236,237] Furthermore in the cohort studies, only those patients who self-selected to return to clinic are represented, and other potential confounders such as timing of NIV, advances in ventilation strategies, pharmacological management and evolution of a multidisciplinary team approach are present.

The earliest, retrospective works represent the clinical practice of two groups; Bach and colleagues, and McKim and colleagues. The four case series published by Bach *et al* describe their cohorts of patients with DMD[216,238] or heterogeneous NMD (including DMD and MND).[208,209] Included are all patients who underwent initial evaluation, which included testing of VC, MIC and/or LIC, PCF and assisted PCF. If VC was less than 70-80% predicted or 2 litres, patients were prescribed LVR three times a day. Those who returned for re-evaluation were monitored with repeat respiratory function testing. If not already performing LVR, it was initiated once the VC criterion was met, or in the case of DMD, once VC plateaued. The published data were obtained from retrospective chart reviews although it is not clear if these papers represent the same data or different patients.

In patients who returned for routine evaluation, it was observed that MIC could improve over time, even in the face of declining VC.[209,216] In one study, VC remained unchanged in those patients who increased MIC over the follow-up period, whereas it fell in patients who also demonstrated a declining MIC. A small but statistically significant improvement in assisted PCF was also reported (222 ± 84 to 258 ± 96 L/min,

difference = 42 ± 66 L/min, p<0.01).[208] The authors' interpretation was that regular LVR can improve respiratory function in the context of progressive NMD, and concluded that this therapy "is indicated for all NMD patients with diminishing VC".[209]

However, these studies have a number of additional limitations which cast doubt on the strength of the conclusions made, namely poorly defined follow-up periods, incomplete datasets and questionable statistical analyses. Furthermore, categorising patients and comparing those who increased versus decreased MIC over time without considering the underlying disease, in a sample of 43 participants with a mixture of rapidly- and slowly-progressive NMDs, introduces a considerable confounder.[208] These papers, representing small and select patient populations, raised the notion that MIC may improve over time in some people with NMD. The authors proposed it signified greater lung and chest wall "range of motion" and resulted in improved cough effectiveness which can decrease the risk of pneumonia.[208] The increase in MIC observed may however reflect a practice effect, rather than a change in respiratory system mechanics. The significant selection-bias also limits interpretation of the results; most patients elected not to return to the clinic (35-72% of the published cohorts had a single assessment only), therefore change in respiratory function is not available for comparison, and may be similar to those who stated they performed LVR routinely.

The work by McKim, Katz and colleagues in people with DMD also suggested a possible long-term benefit of LVR.[136,137] Their initial paper of 22 patients who had been initiated on twice-daily LVR demonstrated a slower rate of FVC decline in the 45 months after therapy commenced compared to the 34 months prior (pre-LVR = 4.7% predicted per year vs post-LVR = 0.5% predicted per year). The authors acknowledged limitations of self-reported LVR use and the potential for NIV use to confound lung function changes, and called for a prospective RCT to support their observational effects and aid translation.[137] The follow-up study of 16 participants from the same cohort for a median of 6 years suggested the improvement in MIC-VC difference was maintained for up to 10 years after LVR initiation, with concomitant stability in PCF. Maximal insufflation capacity also increased slightly during the first 4-5 years post initiation of

LVR. Whilst the authors hypothesised that LVR may preserve C_{rs}, they did not measure this.[136] Nonetheless, the observation that FVC did not significantly fall over time in the setting of worsening MEP values[137] would support the hypothesis that regular LVR may maintain lung and/or chest wall "flexibility".

The same group also examined the effect of LVR in people with multiple sclerosis, and found that of the 35 people who returned to the clinic, the rate of decline of FVC was slower in those who could perform the technique and were prescribed daily LVR, compared to those who were not. Although FVC and PCF values fell, MIC remained stable but did not increase. Participants prescribed routine therapy had lower baseline FVC and unassisted PCF, suggesting that LVR may be more beneficial in people with more restricted pulmonary function.[217] Alternatively, given the LVR group were more severe than those who did not perform LVR routinely, the decline in the latter group may represent natural disease progression, again highlighting the need for prospective controlled data.

Author/s	Year	Number of participants*	Population	Trial design	Therapy and follow-up period	Results
Houser[239]	1971	14	DMD, paed	Randomised matched-pair study	6 minutes IPPB 5 days/week (n=7) *vs.* Control (n=7), for 3 months	No difference in rate of FVC decline
Adams[240]	1974	3	DMD, paed	Case report	Swimming + IPPB program for 11 months	VC improved during program, decreased during vacation periods
Simonds[230]	1989	10	Restrictive CWD	Prospective uncontrolled trial	5 minutes MI (6 participants = volume, 4 = pressure NIV), x2-3/day for 9 months.	No change in VC or TLC overall. Small, statistically significant increase in VC in volume group
Kang[208]	2000	43	MND, Slow NMDs	Retrospective case series (date range not stated)	108 cases (65 single Ax, 43 multiple visits) Prescribed LVR 10-15 inflations 3x/day if VC <2 L Follow-up period not stated	All reported using at least x2/day: 30 / 43 increased MIC over time → VC unchanged, assisted PCF increased 13 / 43 decreased MIC over time → VC and assisted PCF fell
Bach[216]	2007	47	DMD	Retrospective case series (1996 – end date not stated)	78 cases (31 single Ax, 47 multiple visits) Prescribed LVR 10-15 inflations 3x/day Follow-up period 7 – 169 months	31 / 47 reported using at least x2/day: MIC increased, VC fell over time in 31 patients; no comparison with 16 patients who did not perform routinely.
Bach[209]	2008	46	MND, Slow NMDs	Retrospective case series (2005 – end date not stated)	282 cases (204 single Ax, 78 multiple visits) Prescribed LVR 10-15 inflations 3x/day Follow-up period not stated	46 / 78 had follow-up data: MIC and LIC increased, VC fell over time.

Author/s	Year	Number of participants*	Population	Trial design	Therapy and follow-up period	Results
Laffont[232]	2008	14	Recent SCI	Randomised cross-over trial	20 mins IPPB x2/day, 5d/week for 2 months vs Control	No difference in VC, lung volume, dynamic C_L between IPPB or no IPPB periods
McKim[137]	2012	22	DMD	Retrospective cohort study	Prescribed x 2/day LVR: 3-5 maximal inflations / session Compared RFT data pre-LVR (median 34 months) to post-LVR (45 months)	22 reported adherent with x2/day LVR Rate of FVC decline slowed post LVR: pre-LVR 4.7 vs post-LVR 0.5 %pred/year
Srour[217]	2013	35	Multiple Sclerosis	Retrospective case series (1999 – 2010)	79 cases (44 single Ax, 35 multiple visits) Prescribed x 2/day LVR: 5 maximal inflations / session if FVC <80% and trial of LVR improved RFT (MIC > VC) Median follow-up 13 months	Of 35 patients prescribed regular LVR and multiple data: Rate of FVC decline slower in group who achieved PCF_{LVR} > PCF at baseline
Marques[213]	2014	22	Slow NMDs, paed	**Prospective uncontrolled trial**	4-6 months of x 3/day LVR 3-4 maximal inflations / session	18 / 22 completed No change in FVC or MIC. Unassisted and assisted PCF increased
Kaminska[220]	2015	24	MND, Slow NMDs	**Prospective uncontrolled trial**	3-months of x 2-4/day LVR 3-5 maximal inflations / session	19 / 24 completed → 14 willing to continue LVR post study period FVC fell, LIC and LIC – FVC increased over time No change in PCF or QoL

Author/s	Year	Number of participants*	Population	Trial design	Therapy and follow-up period	Results
Rafiq[105]	2015	21 LVR 19 MI-E	MND	**Randomised controlled trial**	1-year of x2/day LVR or MI-E 3-5 maximal inflations /session	Primary outcome = RTI. No difference b/w groups in RTI rate No difference in survival, QoL Adherence: 71% LVR, 53% MI-E
Jeong[241]	2015	14 LVR 12 IS Control	Recent SCI	**Randomised controlled trial**	20 repetitions x2/day: LVR *vs.* incentive spirometry (control); 5 days/week for 6 weeks	FVC and PCF increased over time in both groups, but PCF improvement greater with LVR > Control
Stehling[242]	2015	21	Slow NMD, paed	Retrospective cohort study (2009 – 2012)	3 maximal inflations via MI-E repeated in sets for 10 minutes, x2/day. Analysed VC for 2 years pre and 2 years post initiating MI-E at home	VC increased within the first year post MI-E initiation (mean relative improvement = 28%)
Katz[136]	2016	16	DMD	Retrospective cohort study (1991 – 2008)	Prescribed x 2/day LVR: 3-5 maximal inflations / session Median follow-up = 6.1 years	LIC-VC increased 0.02 L/year LIC increased and FVC stable / rate of FVC decline slowed post LVR: pre-LVR 4.5 *vs.* post-LVR 0.5 %pred/year
Chiou[238]	2017	151	DMD	Retrospective case series (1996 – 2015)	232 cases (81 single Ax, 151 multiple visits) Prescribed LVR 10-15 inflations 3x/day once VC plateaued (53 cases)	151 patients: rate of VC decline = 8.8 % of plateau VC / year (includes 53 below) 53 patients prescribed LVR: rate of VC decline = 8.5% of plateau VC / year
Chatwin[243]	2020	181	Slow NMD	Retrospective case series (2014 – 2018)	181 patients with MI-E at home and prescribed daily use (includes service provision, MI-E criteria, use, settings)	Yearly adherence data on 137: median days used = 60%, 1.8 sessions/day, 2.3 mins/session.

Table 2-7: Studies investigating the effects of regular Assisted Inflation in participants with NMD

Shaded rows highlight studies employing LVR. Trial design notes in **bold** signify prospective studies. * = number of participants with longitudinal data
DMD = Duchenne muscular dystrophy, paed = paediatric cohort, CWD = chest wall disease, MND = motor neurone disease, NMD = neu romuscular disease, SCI = spinal cord injury.
IPPB = inspiratory positive pressure breathing, MI = mechanical insufflation, NIV = non-invasive ventilation, LVR = lung volume recruitment, MI-E = mechanical insufflation-exsufflation.
Ax = assessment, RFT = respiratory function test, VC = vital capacity, FVC = forced vital capacity, TLC = total lung capacity, MIC = maximum insufflation capacity, PCF = peak cough flow, LIC = lung insufflation capacity, C_L = lung compliance, QoL = quality of life, RTI = respiratory tract infection.

Two prospective, uncontrolled studies have examined respiratory function 3-6 months after prescribing LVR in NMD populations naïve to the therapy.[213,220] Dosage was similar in both studies, and was consistent with that used by the McKim and Katz group.[136,137] Marques and colleagues studied younger participants with NMD who were not on NIV (mean age of 15 years, range 7 to 23 years) and found no change over time in FVC or MIC, but an improvement in PCF measures. The authors reported a significant improvement in FVC when 9 patients without scoliosis were analysed separately, however the mean magnitude of this increase was 91 mL (or <5% of baseline)[213] and unlikely to be clinically significant. Adherence was not assessed.

Twenty-four older participants (mean age of 54 years) with a diagnosis of MND, PPS or myotonic dystrophy were investigated by Kaminska *et al*. Adherence diaries, questionnaires assessing QoL and acceptance of LVR were conducted after 3-months of initiating twice-daily LVR. Physiological parameters were analysed according to intention-to-treat, and also for those people who reported performing LVR on average a minimum of twice a day.[220]

There was a small but statistically significant decline in FVC of 82 mL (95% CI = -159, -5 mL) in the 19 patients who completed the study, with a trend to increasing LIC (154 mL (-13, 322 mL)). Consequently the LIC-FVC difference increased over time (243 mL (65, 420 mL)), with a greater magnitude of effect in the 12 participants who reported performing the therapy twice a day (430 mL (126, 558 mL)). No changes were detected in QoL over the three-month period.[220] The authors interpreted this finding to mean the twice-daily exercises did not place additional burden on people's care, however it may also indicate that participants perceived no symptomatic improvement in their health-related QoL. Given only half of the recruited cohort performed LVR as prescribed and ten out of 24 recruited participants were not willing to continue after the study concluded,[220] the latter interpretation may be more likely. The qualitative elements of this feasibility study raise important questions regarding the perceived benefit versus burden of performing therapy trade-off that all individuals consider when undertaking routine exercise.

These themes were also evident in a randomised comparison study comparing a year-long trial of LVR to MI-E in participants with MND. Of the 21 participants in the LVR arm, 71% reported performing two sessions a day, compared to 53% of the MI-E group. Of the 15 participants who did not use a technique as prescribed, 11 had severe bulbar impairment. No change was noted in carer strain or QoL indices. There was a low event rate of RTI in both groups (the primary outcome), and respiratory function analysis was limited to VC and PCF. No differences were noted between groups in the average rate of decline per month. Two major limitations of this study were commencement of assisted inflation therapy at the same time as NIV initiation, a substantial confounder given the impact of NIV on respiratory function, symptoms and QoL in people with MND; and the lack of a control or active control group.[105]

A control group was included in the only other RCT to assess the effect of LVR. Twenty-six patients with cervical SCI were allocated to twice daily LVR or incentive spirometry (active control) for 6-weeks; time from injury is not detailed but is presumed to be new diagnosis and acute-care hospitalisation. Both groups improved FVC over time with no between-group differences. A statistically significant difference was reported in PCF, with the LVR group having a larger improvement (baseline = 204 ± 129 L/min to post = 261 ± 126 L/min) than the incentive spirometry arm (240 ± 142 L/min to post = 249 ± 110 L/min).[241] Again, the clinical significance of an improvement in PCF is unclear, as is the applicability of an acute SCI cohort to medically-stable NMDs.

Collectively, the longer-term studies of LVR critiqued above, plus the additional studies of other therapies briefly summarised in Table 2-7, provide information around feasibility of prescribing regular respiratory physiotherapy, whether it be for a three-month period or decades. What is not well understood is the actual adherence rate; where this has been mentioned it has relied largely upon self-report, and in the case of the retrospective trials, in cohorts of patients who self-selected to return to the same centre. Without knowledge of frequency of exercises, or a comparison group, changes in lung function cannot be fully appreciated. Furthermore, considering that only 50% of recruited patients elected to use LVR more than twice a day in one study,[220] the

burden versus perceived benefit of regular, long-term therapy emerges as a question equally as important as efficacy.

2.8 SUMMARY

Respiratory system impairment, characterised by a reduction in lung volume, is associated with hypercapnia, respiratory failure and the need for nocturnal ventilation in some NMDs. Respiratory tract infections may exacerbate decline. Ultimately, many people with a NMD die of respiratory complications.

Maintaining lung volume, or at least slowing the decline, is one aim of the respiratory management and clinical care of people living with a NMD. Domiciliary NIV is one established line of treatment. In the case of people with MND, NIV slows the progression of respiratory muscle weakness and lung volume decline, improves nocturnal hypoventilation and survival.[4] Other therapies may also prove to be effective adjuncts in treating respiratory issues in people with NMD.

A better understanding of the physiological mechanisms of respiratory dysfunction in NMD may help target adjunctive therapies. Findings from small studies would suggest that loss of lung volume is not solely related to respiratory muscle weakness; decreased respiratory system compliance may also be a contributing factor. Further work in this area is warranted to expand on the existing knowledge base. Particularly, if an association between decreased respiratory system compliance and lung volume was replicated in a larger cohort, this would suggest that there may be a role for therapies that maintain "flexibility" of the lungs and chest wall.

Lung volume recruitment is one technique that may achieve this objective. In people with respiratory muscle weakness and limited capacity to take deep breaths, LVR is an effective method for augmenting lung volume, which may potentially result in a short-term improvement in lung and/or chest wall compliance. Preliminary reports propose that daily LVR can maintain or improve the maximum inflation volume over time, in the context of progressive disease and declining VC. Maintaining recruitable lung volume has been likened to maintaining "range of motion" and respiratory system compliance; shifting the balance between weak respiratory muscles and work of

breathing, thereby potentially attenuating the lung volume restriction common to the NMDs discussed herein.

Whilst this hypothesis seems plausible, there is a lack of physiological studies confirming the immediate effects of LVR in a stable population. Moreover, a growing number of consensus statements and disease-specific treatment recommendations advise regular LVR despite robust evidence of longer-term therapeutic efficacy. Instigating regular treatment has the potential to burden people living with NMD and their carers, hence appropriate evaluation is necessary to ensure clinical recommendations are evidence-based.

2.9 RESEARCH AIMS

The overarching aims of this research project are thus to:

1. describe features of respiratory dysfunction in a group of people living with NMD, and explore the relationships between these elements,
2. evaluate the immediate respiratory effects of a single-session of LVR, and
3. investigate the effect of performing regular LVR on respiratory function, symptoms and quality of life.

2.10 STUDY HYPOTHESES

In line with these general research aims, broad hypotheses are presented below. These will be elaborated on and clearly defined as null hypotheses in the forthcoming chapters.

1. That reduced respiratory muscle strength and respiratory system compliance are both associated with loss of lung volume in people with NMD with respiratory system involvement.

   Given the heterogeneity in rate of disease progression and age at symptom onset, an associated exploratory hypothesis is also put forward: that different relationships exist between lung volumes, respiratory muscle strength, total respiratory system compliance and cough, between people with rapidly-progressive MND compared to other more slowly-progressive NMDs.

2. That a single-session of LVR will result in an immediate improvement in respiratory system compliance and lung volumes.
3. That performing LVR twice daily for a three-month period will improve lung insufflation capacity (the maximal tolerable inflation volume), lung volumes, respiratory system compliance and quality of life.

3 METHODOLOGY

3.1 STUDY OVERVIEW

A prospective, multi-site, single-blinded RCT comparing two types of breathing exercises was performed in people with NMD and respiratory system involvement. The study, titled "Lung Volume Recruitment in Neuromuscular Disease: Can breath-stacking improve lung function, respiratory symptoms and quality of life for people with neuromuscular disease?" (HREC/15/Austin/117) was approved by the Austin Health Human Research Ethics Committee (1st June 2015). Local governance authorisation was obtained from the Research Ethics Office at each of the three sites (Austin Health, Calvary Health Care Bethlehem and The Royal Children's Hospital Melbourne). The study was prospectively registered (1st June 2015) in the Australian New Zealand Clinical Trials Registry (ANZCTR number ACTRN12615000565549). All participants gave written or verbal informed consent (if unable to sign) before inclusion in the trial. A third party witness who was not part of the research team co-signed the verbal consent form. If participants were under the age of 18 years, informed consent was obtained from both the participant and their parent/guardian.

3.2 STUDY DESIGN

This research project comprised three discrete components, embedded within one RCT. Part 1 examined the characteristics of respiratory function and incidence of RTIs in people with a rapidly-progressive NMD, namely MND ("MND" sub-group), and other more slowly-progressive diseases ("Other NMD" or "Other" sub-group). Part 2 investigated the immediate physiological effects of performing a single-session of LVR on respiratory function. Part 3 comprised a parallel arm, active-controlled trial of regular LVR, prescribed twice-daily for a three-month period (Figure 3-1).

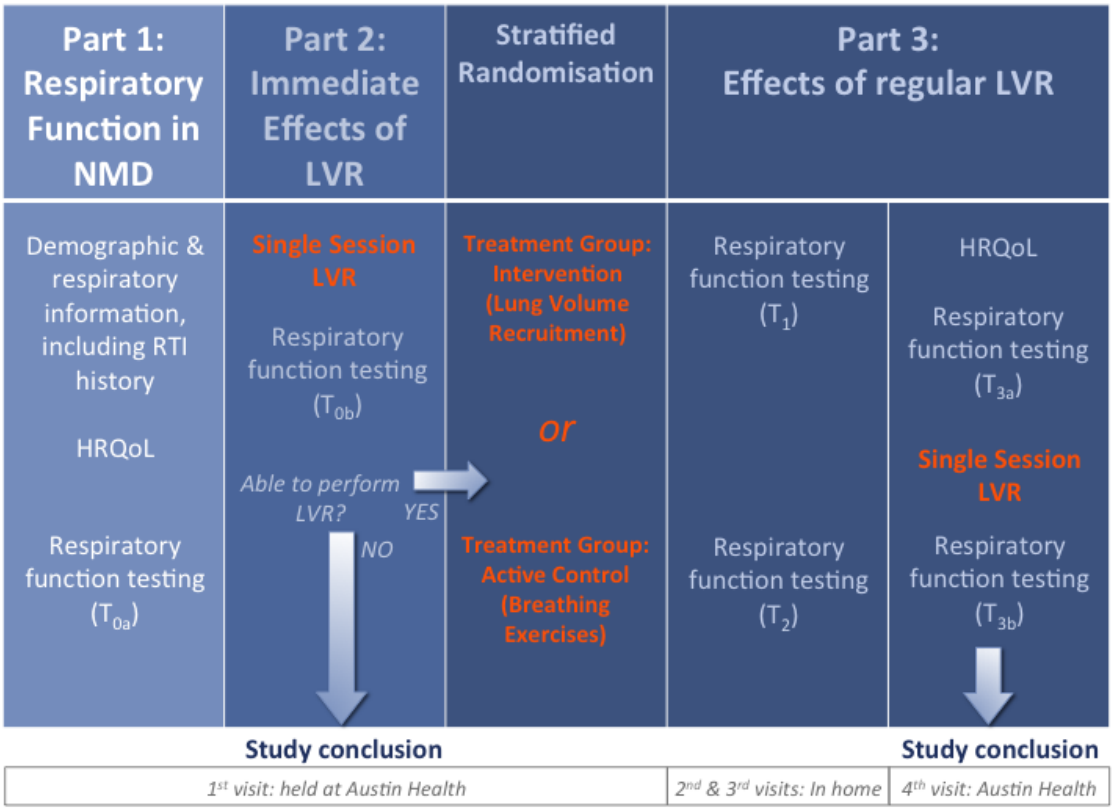

Figure 3-1: Study design and timepoints

RTI = respiratory tract infection, HRQoL = health-related quality of life, LVR = lung volume recruitment, Tx = Timepoint x

3.2.1 STUDY TIMEPOINTS

The first study visit (Timepoint 0) comprised two separate assessment sessions on the same day (Timepoint 0a and 0b). Timepoint 0a involved collection of demographic and respiratory information (including past history of RTI), health-related quality of life (HRQoL) measures and baseline respiratory function (see Figure 3-1: Part 1). Following a 45-minute rest period, a single-session of LVR therapy was conducted and respiratory function testing repeated (Timepoint 0b).

If participants met the pre-defined randomisation criterion (Section 3.4.1), they were randomly allocated to one of two treatment groups for the RCT: the Intervention arm

(LVR) or Active control arm (Breathing exercises). If the randomisation criterion was not met, participation in the study concluded with a clinical review to assess indication for ongoing physiotherapy as per usual clinical care.

Follow-up visits for the RCT were conducted at one-month (Timepoint 1) and two-months (Timepoint 2) post-randomisation in participants' homes, to minimise the burden of study participation and to maximise participant retention. The study's final visit occurred three-months post-randomisation (Timepoint 3). Participants repeated the respiratory function testing and HRQoL assessment (Timepoint 3a). After a 45-minute rest period, a single-session of LVR therapy was conducted in all participants regardless of treatment group, followed by repeated measurement of respiratory function (Timepoint 3b) (Figure 3-1).

3.3 PARTICIPANTS

Participants were recruited from three sites: i) the state-wide provider of adult domiciliary ventilation (the Victorian Respiratory Support Service (VRSS)) based at Austin Health, Melbourne, Victoria, Australia (Victorian population ~5.5 million); ii) outpatient clinics of Calvary Health Care Bethlehem, the state's largest specialised multidisciplinary service for adults with a progressive NMD and iii) the paediatric neuromuscular outpatient clinic at The Royal Children's Hospital Melbourne.

3.3.1 STUDY INCLUSION AND EXCLUSION CRITERIA

People >14 years old, with a diagnosis of NMD or chest wall disease of at least three months duration *and* respiratory system involvement, defined as a FVC <80% of predicted normal,[244] were eligible to participate. Details of domiciliary NIV prescription and use were collected, but NIV was neither an inclusion nor an exclusion criteria. If participants did use NIV, they were required to be established on ventilation for at least three months prior to study entry, as recent implementation of ventilatory assistance may potentially confound any observed changes in lung function, symptoms or quality of life.

Exclusion criteria were:

- previously prescribed daily LVR therapy performed for more than six consecutive weeks within the past six months, or three months within the last year. Lung volume recruitment therapy was defined as LVR using a resuscitation bag, ventilator or glossopharyngeal breathing, or MI-E. Use of these interventions for occasional cough augmentation (without cycles of maximal inflation) or during an acute RTI were not criteria for exclusion;
- inpatient admission for an acute respiratory issue within the preceding six weeks;
- contraindications or precautions for the use of positive pressure therapy, including previous history or perceived risk factors for pneumothorax, active haemoptysis, bullous emphysema, recent eye surgery;
- invasive ventilation via tracheostomy;
- medical instability;
- non-proficiency in English;
- inability to provide informed consent.

3.3.2 RECRUITMENT PROCEDURE

Potential participants were identified at routine outpatient clinic appointments or other clinical reviews by their treating clinician, who obtained verbal consent for contact by the study co-ordinator. In addition, a search of the clinical database of the VRSS identified people with NMD. Potential participants were posted a letter of invitation, asking them to contact the study co-ordinator if they were interested in receiving further information about the study. The study co-ordinator was independent of usual clinical care and conducted all recruitment discussions, detailing study objectives, design, interventions and eligibility. Interested participants were provided with the trial Patient Information and Consent Form (PICF) at least 48 hours prior to study enrolment. A second verbal explanation of the study was provided prior to PICF signing. Signed copies of the PICF were provided to each participant and placed in their medical record.

3.4 RANDOMISATION

3.4.1 RANDOMISATION CRITERION

To proceed to randomisation, participants were required to demonstrate that they could effectively perform the intervention. This was defined as assisting inflation above the greatest unassisted spontaneous breath possible, that is, achieving a LIC greater than VC, by at least 10% ((LIC minus VC difference / VC) multiplied by 100) (D McKim, *personal communication*).

3.4.2 RANDOMISATION PROCESS

Underlying respiratory mechanics may be different between people with rapidly-progressive disease such as MND and other, more slowly-progressive conditions, and as such the response to therapy may be quite disparate. Accordingly, allocation to treatment group was stratified by disease sub-group defined *a priori*, namely "MND" or "Other NMD". A research assistant not involved with the research project created a computer-generated block randomisation sequence (www.randomization.com) and transferred this to individually numbered, sealed opaque envelopes. Block size was not disclosed to the research team (variable blocks of 4 or 6). Envelopes were opened sequentially by the unblinded study assessor, if the randomisation criterion was met during Timepoint 0.

3.5 TREATMENT GROUPS

Participants were randomly allocated to one of two types of breathing exercises prescribed twice-daily, for the three-month period. The treatment groups were: the Intervention arm comprising LVR; and the Active control group of Breathing exercises. "Sham-LVR" was not feasible; this would require a resuscitation bag that did not produce airflow when compressed, and participants would be acutely aware they were not receiving air via the mouthpiece. Using a smaller volume bag or pressure-release valve to minimise airflow were considered, however this would still produce lung inflation and LVR would be possible if many bag compressions were performed in quick succession. Hence rather than sham-LVR, the treatment arms were matched for participant-to-therapist interaction, follow-up and exercise dose.

3.5.1 STANDARDISED PRESCRIPTION GUIDELINE

To standardise the treatments and prescription goal for this RCT, a treatment guideline was needed. Regular LVR dosage is ambiguous and variable in the literature, with cumulative daily dose ranging from 4 to 45 maximal inflations. Prescriptions range from three to five breaths per maximal lung inflation for a total of 3-5 cycles conducted twice[136,137,217] or up to four times[213,220] a day, to 10-15 maximal lung inflations performed three times per day.[170,208,209,216] Ill-defined terminology also creates confusion; one study states that "patients were trained to use 2-3 cycles of breath-stacking per session, stacking 3-5 breaths per cycle".[105] This could be interpreted as 2-3 assisted inflations comprising 3-5 bag compressions each, or 3-5 assisted inflations performed 2-3 times per session.

The "FITT" principle of exercise training was therefore used as a framework[245,246] (Table 3-1). In this schema, *Frequency* refers to the number of sessions performed over a defined time period, for example per day or week. *Intensity* refers to how difficult or vigorous an exercise is; in the case of breathing exercises, this refers to the "depth" or volume of inspiration or inflation reached. *Type* relates to the nature of the exercise,

that is LVR or the active control breathing exercises, whilst *Timing* is defined as the duration of exercise conducted in a single session, expressed in minutes or the number of repetitions and sets.[246] The number of compressions or insufflations required to reach maximal inflation is an additional variable needed for LVR dose, individually titrated based on chest wall excursion, patient comfort and pressure level reached.

Elements of the active cycle of breathing technique (ACBT)[247] were also incorporated into the target dosage. Typically, the ACBT consists of: four to six relaxed breaths ("breathing control"), followed by three to six deep breaths ("thoracic expansion exercises"), another period of breathing control and then one to two huffs.[248-250] This cycle is repeated until expectoration of sputum is complete, hence the number of "sets" performed varies depending on sputum load.[248,250]

Principle	Detail
Type	LVR or Breathing exercises
Intensity	LVR: to maximal tolerated insufflation capacity Breathing exercises: a "slow, deep breath"
Timing – repetitions	Up to five breaths, followed by relaxed tidal breathing for 30-60 seconds
Timing – sets or session duration	LVR: repetitions repeated for five sets Breathing exercises: repetitions repeated for 10-minutes
Frequency	Minimum of two sessions per day, seven days a week
Position	Exercises performed in the sitting position unless otherwise stated

Table 3-1: Standardised exercise prescription for RCT treatment groups

LVR = lung volume recruitment

Using this standardised prescription guideline, the allocated treatment was explained during a one-on-one training session of approximately 20 minutes duration, at the conclusion of Timepoint 0. All one-on-one sessions were conducted by one of two experienced respiratory physiotherapists (LR or CC), who specialise in the respiratory management of people living with a NMD and/or severe ventilatory compromise. Each participant received an instruction booklet with their individualised prescription and a daily usage diary.

3.5.2 INTERVENTION ARM – LUNG VOLUME RECRUITMENT

Participants were advised to use LVR at least twice per day, with a target prescription of 5 sets of 5 maximal inflation repetitions per session (Figure 3-2). Definitions of LVR terminology are given in Table 3-2.

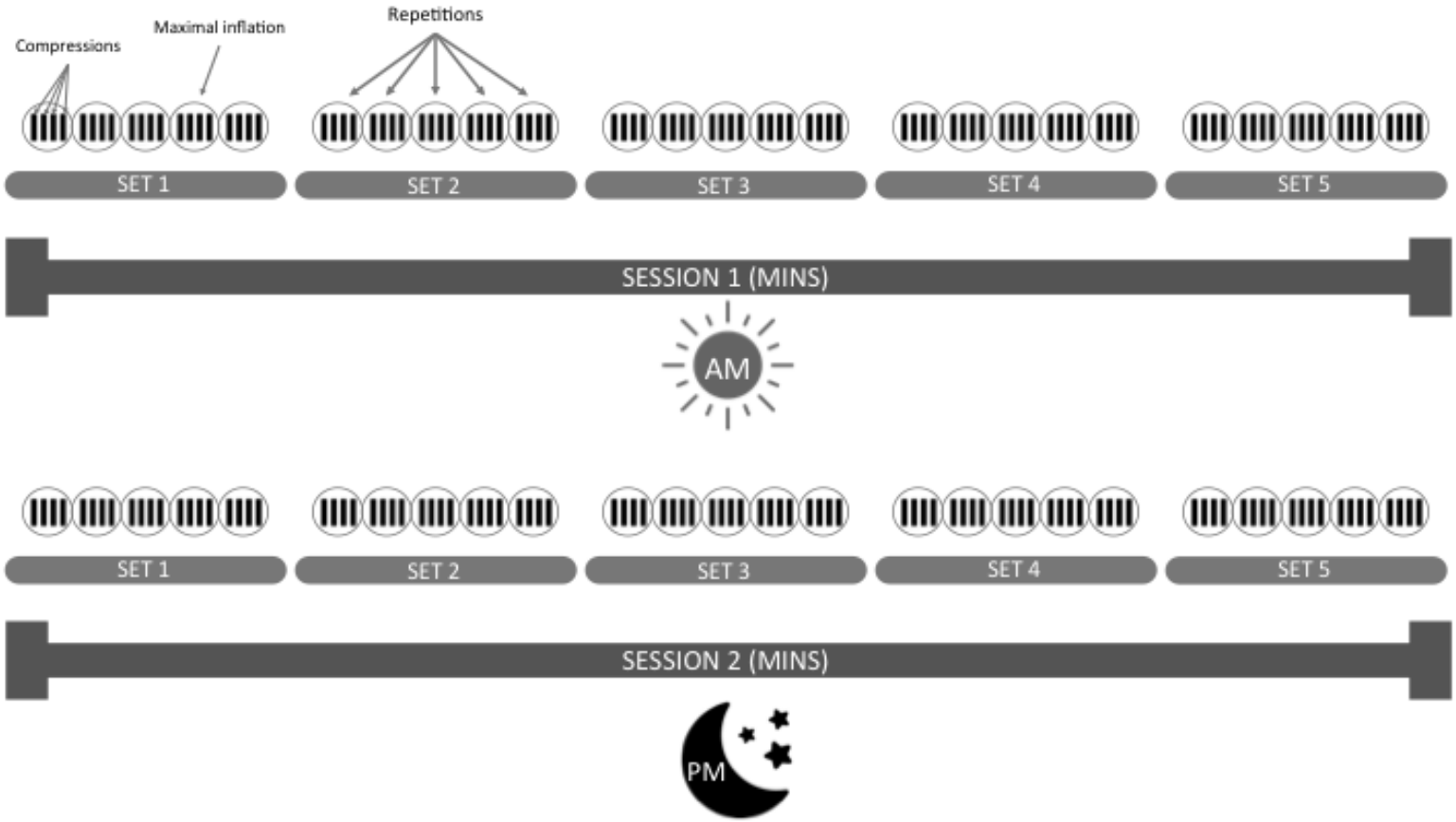

Figure 3-2: Schematic illustration of the target LVR daily dose

LVR = lung volume recruitment. The target prescription was five sets of five maximal inflations, performed twice per day. The number of compressions per maximal inflation was tailored to each individual and checked with a manometer to ensure peak inspiratory pressure did not exceed 50 cmH_2O; the four compressions depicted in the illustration is representative only.

Terminology	Definition	Study specific
Insufflation (also known as "Compression" if delivered by a resuscitation bag)	An inspiratory volume of air. For single-breath maximal inflation methods, one insufflation achieves LIC. E.g. NIV (PCV mode), IPPB or MI component of a MI-E device. For stacked-breath maximal inflation methods, multiple insufflations or compressions are required to reach LIC or MIC. E.g. glossopharyngeal breathing, compressing a resuscitation bag / LVR kit, or LVR via VCV-NIV.	Insufflation can be from FRC or IC. If from FRC: insufflations can be delivered passively *or* with the person actively assisting. If from IC: the person is instructed to inspire fully, then insufflated from their IC to LIC. The number of resuscitation bag compressions (insufflations) required to reach the maximum, tolerable insufflation capacity is determined by visual inspection of chest wall excursion and patient comfort. Peak inspiratory pressure must be measured and not exceed 50cmH_20.
A repetition (rep)	One complete maximal inflation (also known as a MIC or LIC breath)	Number of compressions required to achieve maximal inflation is individualised, however as a guide: if starting from FRC: 5 to 10 compressions; IC: 1 to 3 compressions. A brief breath-hold at LIC (~ 1-3 seconds) can be incorporated. Exhalation is passive to FRC.
Set	A series of repetitions performed sequentially	**Aim for 5 maximal inflation repetitions per set**. Between reps, a few spontaneous tidal breaths may be performed.
Dose	The number of maximal inflations prescribed per session (reps x sets)	**Aim for 5 sets of 5 reps.** Between sets, spontaneous tidal breathing for 30-60 seconds is recommended.

Table 3-2: Standardised nomenclature for LVR therapy prescription

LVR = lung volume recruitment, LIC = lung insufflation capacity, MIC = maximal insufflation capacity, NIV = non-invasive ventilation, PCV = pressure control ventilation, IPPB = inspiratory positive pressure breathing, MI = mechanical insufflation, MI-E = mechanical insufflation-exsufflation, VCV-NIV = volume-limited (i.e., volume-controlled ventilation) mode of NIV, FRC = functional residual capacity, IC = inspiratory capacity.

A commercially-available LVR kit (LVR kit item number 1034502; Mercury Medical®; Florida, USA) was used to perform LVR. This comprised an adult 1.6 litre manual resuscitation bag, one-way in-line valve, mouthpiece and nose clip. An oro-nasal mask was provided if participants were unable to maintain a seal around the mouthpiece (Figure 3-3). A custom-built LVR counter was fitted to each LVR kit, which participants turned on prior to each session to objectively record LVR usage (Section 4.5: LVR counter design and operation).

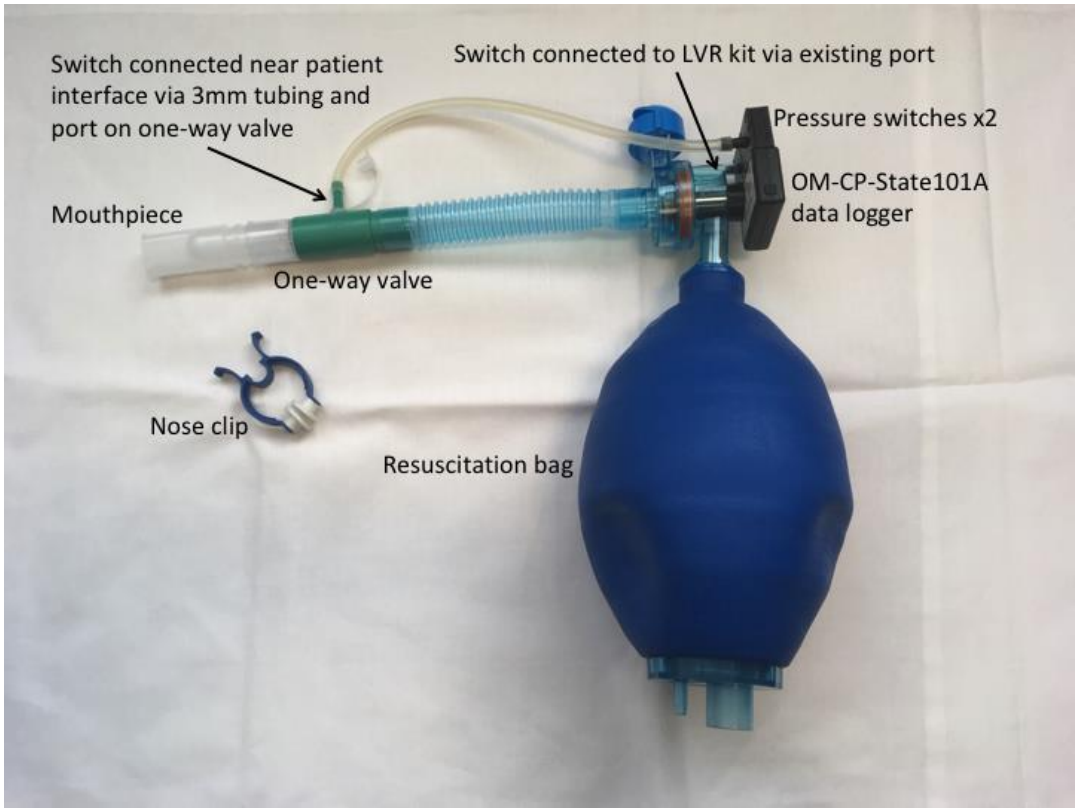

Figure 3-3: Lung Volume Recruitment kit, complete with fitted LVR counter

To perform LVR, participants were instructed to compress the resuscitation bag to assist inspiration ("stack"), then hold the inspired volume of air by keeping a firm seal around the mouthpiece or oro-nasal mask, then stack again. Insufflations typically commenced from FRC and were repeated until the person reached their maximum tolerable insufflation capacity (LIC). A passive exhalation to FRC completed the maximal inflation manoeuvre, which was also termed a "LIC breath".

The number, speed and volume of resuscitation bag compressions necessary to reach LIC for each individual participant was titrated by the respiratory physiotherapist conducting the one-on-one training session. This was based on chest wall excursion, breathing pattern, comfort, dyspnoea, fatigue or symptoms of hypotension or hyperventilation. Peak inspiratory pressure was measured with a manometer placed in-line to ensure that pressure did not exceed 50 cmH_2O. This was checked at each subsequent study visit.

Two to four tidal breaths were encouraged before commencing the next maximal inflation repetition. If participants were advised to perform less than the five target repetitions per set initially, the aim was to gradually increase to the standardised upper limit if tolerated. A rest period of relaxed tidal breathing for 30 seconds (longer if required) was interspersed between sets. Again, participants were instructed to gradually increase the number of sets to five per session, but had clear instructions regarding stopping or adjusting therapy in the presence of unexplained pain, dizziness, breathlessness or concern.

Use of LVR for cough augmentation was not incorporated into the prescribed routine LVR session, however participants were advised that they could use LVR for this purpose as required. Participants were asked to document any LVR use in their self-report diary, plus ensure the LVR counter was operational whenever LVR was performed (Section 3.7.11).

Strategies to facilitate independent LVR were used where possible. For example, if proximal upper limb function limited compression of the resuscitation bag by hand, options of compressing the bag against a firm surface, between knees or under their armpit were trialled. Tubing length between bag and interface was a standard six inches (15.2 centimetres) long but was extended depending on the participant's technique and position. In some cases, participants required assistance from their carers to perform the technique.

3.5.3 ACTIVE CONTROL – BREATHING EXERCISES

Breathing exercises were adapted from the ACBT and diaphragmatic breathing patterns used in other areas of physiotherapy practice,[249,251,252] and modified to approximate the dose delivered to the Intervention group.

Participants were instructed to relax any accessory muscle use. A slow, deep inhalation over three to five seconds, focusing on abdominal movement rather than upper ribcage or accessory muscle use, was the aim. Participants were not coached to deep breathe to maximal inspiration. Slow, passive exhalation to FRC followed. This pattern was termed one "diaphragmatic breath".

As per the intervention arm, participants were instructed to perform five repetitions of their allocated exercise, inserting a few spontaneous tidal breaths between each repetition if necessary to avoid dyspnoea or fatigue. A longer rest period of spontaneous tidal breathing (approximately 30-60 seconds) was recommended between sets. The active control was intended to be comparable in time to the intervention arm, hence participants were instructed to perform a *minimum* of 5 sets of 5 diaphragmatic breaths and continuing for up to 10 minutes, at least twice per day.

All participants randomly allocated to the active control arm could perform the breathing exercises without physical assistance.

3.6 Overview of Outcome Measures & Schedule of Data Collection

Primary, secondary and exploratory outcome measures were defined *a priori* (Table 3-3). The change in maximum, tolerable insufflation capacity achieved by breath-stacking using an LVR kit with a one-way valve in situ (LIC) was selected as the primary outcome of interest for the three-month RCT. Secondary outcome measures of VC, the LIC – VC difference, PCF, PCF from LIC (PCF_{LIC}), static lung volumes, C_{rs}, respiratory muscle strength markers, HRQoL and use of prescribed treatment were also selected to inform the research hypotheses. Side effects and hospitalisation rates in the study period were exploratory outcomes of interest.

Primary outcome measure	Lung insufflation capacity (LIC)
Secondary outcome measures	Vital capacity (VC) LIC minus VC difference (LIC – VC) Total respiratory system compliance (C_{rs}) Static lung volumes
Tertiary outcome measures	Peak cough flow (PCF), unassisted PCF from lung insufflation capacity (PCF_{LIC}) PCF_{LIC} minus PCF difference (PCF_{LIC} – PCF) Markers of respiratory muscle strength: ▪ maximal inspiratory pressure (MIP) ▪ maximal expiratory pressure (MEP) ▪ sniff nasal inspiratory pressure (SNIP) Health-related quality of life (HRQoL) ▪ Assessment of quality of life – 8D (AQoL-8D) ▪ Severe respiratory insufficiency questionnaire (SRI) ▪ Revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) Use of prescribed treatment
Exploratory outcome measures	Side effects of treatment and adverse events Hospitalisation rate

Table 3-3: Study outcome measures

Table 3-4 details the data collection schedule. Demographic information collected at Timepoint 0a included gender, age, height (or arm span[253]), weight, diagnosis, time since symptom onset, and presence of gastrostomy. Respiratory information collected at Timepoints 0a and 3a comprised NIV use (none, nocturnal, daytime), current respiratory therapy, use of cough augmentation techniques and self-reported incidence of RTI within the past 12 months. This was defined as primary-care *or* hospital-inpatient diagnosed RTI, with antibiotic use. Respiratory function tests for all study timepoints were performed in the standardised order illustrated in Table 3-4.

All respiratory function and HRQoL outcome measures were collected by assessors blinded to treatment group allocation. The study's primary assessor (NS) conducted all assessments at Timepoints 0a, 0b, 3a and 3b. Home visits (Timepoints 1 and 2) were conducted by the primary assessor or one of three trained, blinded assessors.

Review of treatment technique (and measurement of inspiratory pressure achieved with LVR), usage, concordance with exercise prescription and side effects of treatment were collected by an unblinded assessor each month. The experienced respiratory physiotherapist/s provided additional clinical support as required, and reviewed each participant at the conclusion of the study to determine ongoing physiotherapy as per usual clinical care.

	Timepoint 0a	Timepoint 0b	Timepoint 1	Timepoint 2	Timepoint 3a	Timepoint 3b
Time	Time 0, Ax (a)	Time 0, Ax (b)	1-month	2-month	3-month, Ax (a)	3-month, Ax (b)
Location	Austin Health		Participant's Home	Participant's Home	Austin Health	
Duration	5-6 hours		2-3 hours	2-3 hours	5-6 hours	
Measures						
Demographic information	✓				✓	
Respiratory information	✓				✓	
VC	✓	✓	✓	✓	✓	✓
PCF	✓	✓	✓	✓	✓	✓
FVC, FEV_1	✓				✓	
MIP, MEP, SNIP	✓				✓	
Static lung volumes	✓	✓	✓	✓	✓	✓
C_{rs}	✓	✓	✓	✓	✓	✓
LIC	✓	✓	✓	✓	✓	✓
PCF_{LIC}	✓	✓	✓	✓	✓	✓
SRI	✓				✓	
AQoL-8D	✓				✓	
ALSFRS-R	✓if MND				✓if MND	
Other		Randomised Training session	Treatment review	Treatment review		Treatment review Usual care session

Table 3-4: Schedule of data collection

Ax (a) = pre-session assessment, Ax (b) = post-session assessment, VC = vital capacity, PCF = peak cough flow, FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 second, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure, SNIP = sniff nasal inspiratory pressure, C_{rs} = respiratory system compliance, LIC = lung insufflation capacity, PCF_{LIC} = peak cough flow from lung insufflation capacity, SRI = Severe Respiratory Insufficiency questionnaire, AQoL-8D = Assessment of Quality of Life questionnaire, ALSFRS-R = Revised Amyotrophic Lateral Sclerosis Functional Rating Scale, MND = motor neurone disease.

3.7 Outcome Measures – Definitions and Data Collection Procedures

The level of physical impairment that accompanies many NMDs often renders laboratory-based respiratory physiology testing unsuitable for this population. Ambulatory methods were desired to enable measurement in participants' homes, hence equipment was specifically designed for this project. The LIC, VC, PCF, PCF_{LIC} and C_{rs} were measured using a laboratory-grade system; static lung volumes and markers of respiratory muscle strength were conducted on a commercially-available portable pulmonary function testing system (Hyp'Air Compact Plus® Portable PFT System; Medisoft, Sorinnes, Belgium). Details of equipment, software programming, circuit design, calibration, signal analyses and results of pre-data collection bench-test experiments are provided in Chapter 4.

Calibration was performed immediately prior to each testing session, across the range of flow rates anticipated (Section 4.1.2) and measurement devices underwent weekly biological control testing. Room temperature and relative humidity were measured at each study visit using a whirling hydrogometer (Sling Psychrometer, product code IC736700, instrumentchoice.com.au) to correct for differences in gas volume between ambient conditions (ambient temperature, pressure (ATP)) and conditions in the lungs (body temperature, pressure, saturated with water vapour (BTPS)).

All testing was performed according to American Thoracic Society / European Respiratory Society recommendations where available,[97,254,255] however acceptability of tests was modified to allow for a minimum of two acceptable and reproducible manoeuvres if fatigue prevented three trials (between-manoeuvre repeatability criteria maintained). Similar modifications have been incorporated into respiratory function testing for people with significant respiratory muscle weakness due to SCI, without impairing test reliability or reproducibility.[256,257] Tests were performed in the seated position, without an abdominal binder or wheelchair seatbelt to control for the effects of these on respiratory function in people with respiratory muscle weakness.[258-260]

3.7.1 LUNG INSUFFLATION CAPACITY (LIC)

Lung insufflation capacity is the maximum, tolerable insufflation capacity achieved with external assistance that does not involve the person controlling their glottis (i.e., holding their breath). It is measured on expiration from the upper limit of the assisted inflation manoeuvre, which is provided via i) stacked breaths using a LVR kit or ii) a single-breath inflation delivered via a NIV, IPPB or MI-E device. The volume of air fully exhaled (i.e., to RV) is recorded.[10]

The testing procedure was explained to participants prior to commencement. Participants were instructed to breathe gently (i.e., spontaneous tidal volume breaths) via the measurement circuit using a mouthpiece (with nose clip in situ) or oro-nasal mask if lip seal was not maintained (Circuit Design, Section 4.3). Three to five breaths occurred through the circuit with the spontaneous limb open. After exhaling to approximate FRC, the blinded assessor manually operated the circuit tap to enable communication between the inflation and participant limbs, and commenced compressions of the resuscitation bag. The assessor observed the participant's respiratory pattern (respiratory muscle use and chest wall movement) and real-time respiratory signal traces to ensure bag compressions were coordinated with respiration. The participant was asked to relax their own breathing once breath-stacking commenced, and the assessor communicated each compression with verbal coaching. If this technique was not successfully (e.g. discomfort, reflexive glottic closure), participants were asked to actively inspire with each compression.

The upper limit of the manoeuvre was determined by either the participant or the assessor. Participants were instructed to signal to the assessor once they reached their maximum, tolerable insufflation capacity. Alternatively, the assessor gauged this based on resistance felt in the resuscitation bag; plateauing chest wall excursion; diminishing flow and volume signals with each consecutive bag compression; or when the upper pre-defined pressure limit of 50 cmH_2O was reached. Once LIC was reached, the tap was returned to the starting position, opening the spontaneous limb. Participants were instructed to exhale fully and actively until maximal exhaled volume was reached (i.e.,

to RV). This manoeuvre was repeated a minimum of three times, with a rest period of approximately 30 seconds (longer if required) between each.

The LIC value was determined from the raw signals obtained (Signal Analyses, Section 4.4.1), and represented the difference between the maximum assisted inflation volume and the lowest volume recorded on the subsequent exhalation. The largest, technically acceptable LIC value at each timepoint was used in analysis.

3.7.2 VITAL CAPACITY (VC)

Vital capacity is defined as the maximal volume of air exhaled during an expiratory effort from a maximal inspiration, ending at complete expiration (i.e., RV).[47,97] Exhalation can be forced and rapid (FVC), or slow (SVC). Given it is a voluntary, spontaneous, unassisted manoeuvre it is dependent upon participant effort, and is a function of total respiratory system compliance, inspiratory and expiratory muscle strength. In patients with MND, SVC and FVC are strongly correlated,[261,262] however SVC is considered easier to perform in the context of severe respiratory or bulbar dysfunction.[263] In this study, the ATS/ERS procedure for (slow) VC was followed.[97]

Participants breathed through the measurement circuit via a mouthpiece (with nose clip in situ) or oro-nasal mask if mouth leak was evident (Section 4.3). The participant was instructed to commence spontaneous tidal breathing and then when ready, inhale maximally to TLC. Exhalation at a relatively constant flow was encouraged, in a relaxed but not unduly slow manner, until completely empty (i.e., to RV). Commensurate with the measurement of LIC, the VC value was calculated as the difference between the maximum inspired volume achieved during this maximal spontaneous breath, and the lowest volume recorded on the subsequent exhalation.

The largest, technically acceptable value, with $\leq$150 mL difference between trials, or $\leq$100 mL difference if VC $\leq$1.0 L, was used in analysis.[97] If trials varied more than the 100-150 mL criterion, subsequent trials were performed as tolerated. This absolute value was also expressed as a percentage of predicted normal values.[244,264]

3.7.3 LIC MINUS VC DIFFERENCE (LIC – VC)

The LIC – VC difference is the amount of volume that can be insufflated above VC (the "recruitable volume"). It is calculated by subtracting the VC from the LIC obtained at the same measurement timepoint.

3.7.4 PEAK COUGH FLOW (PCF)

Peak cough flow is defined as the peak expiratory flow rate measured during a cough. Participants performed tidal volume breathing through the measurement circuit via an oro-nasal mask and, when ready, produced their "biggest, strongest" unassisted cough (Section 4.3). A minimum of three trials were conducted, with the largest PCF value used in analysis.

3.7.5 PEAK COUGH FLOW FROM LUNG INSUFFLATION CAPACITY (PCF_{LIC})

Peak cough flow obtained with assistance is defined according to the type of augmentation provided ($PCF_{assisted}$). In this study, the peak expiratory flow rate from the "maximum, assisted inspiratory volume obtained from LIC (PCF_{LIC})"[10] was measured.

Participants breathed through the measurement circuit via an oro-nasal mask (Section 4.3). The same procedure was followed as for the measurement of LIC, however instead of instructing participants to exhale fully and actively to RV, they were asked to give their "biggest, strongest cough". This manoeuvre was repeated a minimum of three times, with a rest period of approximately 30 seconds (longer if required) between each.

A minimum of three trials were conducted, and the peak expiratory flow reached during the cough manoeuvre (PCF_{LIC}) recorded. The largest PCF_{LIC} value was used in analysis.

3.7.6 PCF_{LIC} MINUS PCF DIFFERENCE (PCF_{LIC} – PCF)

The PCF_{LIC} – PCF difference is the difference in peak expired flow rates between coughing from an assisted inflation lung volume above VC, and an unassisted cough. It is calculated by subtracting PCF from PCF_{LIC}, obtained from the same timepoint.

3.7.7 TOTAL RESPIRATORY SYSTEM COMPLIANCE (C_{RS})

Total respiratory system compliance is defined as the change in volume for a change in pressure, across the respiratory system. It refers to the distensibility of the respiratory system as a whole, as distinct from the compliance of the lung (C_L) or chest wall (C_{CW}) in isolation.

Unlike other outcome measures used in this research trial, C_{rs} has not been widely used or reported in participants with NMD. Therefore, a dedicated section describing the testing procedure, derivation and validation of scoring rules for signal analysis is presented in Chapter 5. The summary C_{rs} value was determined and used in analysis, expressed in absolute units. Specific compliance was calculated by dividing the summary C_{rs} value by FRC.[265]

3.7.8 STATIC LUNG VOLUMES: MULTI-BREATH NITROGEN WASHOUT

Static lung volumes (VC, FRC, TLC, IC, RV and ERV) were measured to evaluate compartmental lung volume treatment effects (Figure 2-2, Section 4.2). As per American Thoracic Society/European Respiratory Society recommendations, three technically acceptable tests were performed where possible. If FRC varied +/-25% from the median, that test was excluded and a fourth test conducted if fatigue allowed.[47,254] Where fatigue prevented three or more trials, data from two trials was reported if FRC agreed within 10%.[47] A waiting time of twice the washout duration[254,266] or 15 minutes[47] was observed between tests (whichever was greater).

The highest recorded VC, mean FRC, TLC and IC were reported. Residual volume was calculated as mean TLC minus largest VC. Expiratory reserve volume was calculated as

mean FRC minus RV.[47] Static lung volumes were expressed in absolute units and as a percentage of predicted normal values.[267] Compartmental lung volumes (IC, ERV, RV, FRC) were also expressed as a ratio of each participant's absolute TLC at that timepoint (e.g. IC % TLC).

3.7.9 RESPIRATORY MUSCLE STRENGTH (MIP, MEP, SNIP)

Estimates of respiratory muscle strength were obtained by performing maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP) and sniff nasal inspiratory pressure (SNIP) tests.

Maximal inspiratory pressure and MEP represent the maximum pressure sustained for 1 second at the mouth (P_{mo}), during an isometric inspiratory or expiratory maximal voluntary effort. Under these conditions, P_{mo} reflects the change in P_A produced by respiratory muscle contraction and hence is a marker of respiratory muscle output. The SNIP test measures nasal pressure (reflecting nasopharyngeal pressure) which is similarly an indicator of P_A, during a maximal "sniff" manoeuvre.[255] All measurements of respiratory muscle strength were performed on the pulmonary function testing system.

For MIP and MEP, a small leak was introduced into the circuit using the device's MIP/MEP adaptor to prevent glottic closure and reduce the use of buccal (cheek) muscles.[255] For the MIP manoeuvre, the participant was coached to exhale fully to RV then produce a maximal inspiratory effort. The MEP manoeuvre required a deep breath in to TLC, followed by a maximal expiratory effort with the assessor supporting the participant's cheeks. During both manoeuvres, the device initiated an occlusion of 3000 ms in order to block airflow and thus generate an isometric contraction. The maximum pressure sustained for 1000 ms was recorded. Where required, the assessor pinched the participant's lips around the mouthpiece to maintain an adequate seal. Standard mouthpieces were used as predicted normal reference values were collected with such interfaces[264] and these are preferred for research studies[255].

At least three MIP and three MEP manoeuvres were attempted (if participant fatigue allowed), with a minimum 30 seconds rest between each test. The largest of these three values that varied by less than 20% was recorded.[255] This absolute value was also expressed as a percentage of predicted normal values.[264]

Sniff nasal inspiratory pressure was measured using a nasal cannula with nasal pillow, wedged into each nostril in turn. A validation duration of 500 ms was set to ensure that manoeuvres were less than 0.5 seconds.[268] Participants were instructed to sniff maximally and quickly through the contralateral unobstructed nostril from FRC, as per manufacturer's instructions. At least three attempts per nostril (minimum total of six) were made to achieve a plateau of pressure values, with a rest between each attempt.[255] The largest value was recorded in absolute units and also expressed as a percentage of predicted normal values.[268]

3.7.10 HEALTH-RELATED QUALITY OF LIFE MEASURES

Health-related quality of life questionnaires were included to assess the impact of the participants' chronic condition and the effect of the treatment on their QoL. One generic (Assessment of Quality of Life 8D, AQoL-8D) and one disease-specific (Severe Respiratory Insufficiency, SRI) questionnaire were selected. These were completed at the first and final study visits (Timepoint 0a and Timepoint 3a). In addition, a disease-specific functional rating scale was conducted on participants diagnosed with MND at Timepoints 0a and 3a (the Revised amyotrophic lateral sclerosis functional rating scale, ALSFRS-R).

The AQoL-8D and SRI questionnaires were completed by the participant, with physical assistance provided by a research assistant if required, whereas the ALSFRS-R was administered by the study's primary blinded assessor in consultation with the participant and their caregiver if present.[269] De-identified responses were entered into the electronic web-based database by an unblinded assessor, who communicated with a participant's medical treating team if at-risk mental health concerns were identified.

3.7.10.1 Assessment of Quality of Life 8D (AQoL-8D)

The AQoL-8D is a 35-item, generic multi-attribute utility instrument incorporating eight domains of health. Unweighted profile scores represent each of the domains and a total AQoL score can be calculated, providing a psychometric measure of HRQoL. The standardised psychometric score gives a value between 0 and 100, with higher scores representing better health. Comparison of unweighted scores is not valid, however changes in scores over time can be used as a stand-alone measure (aqol.com.au/index.php/allfaqs). Derived weighted scores produce dimension-specific health state utilities and a global health utility index, calculated using the AQoL-8D utility algorithm (aqol.com.au/index.php/scoring-algorithms). These weighted scores range from 1.00 (full health) to -0.04 (health state worse than death) with 0.00 representing health state equivalent to death, and allow comparison across different health states, rather than simply a classification or description of a cohorts' QoL.

Within the AQoL-8D model, three dimensions or domains (independent living, pain and senses) map to the super dimension of "Physical Health". Five dimensions (mental health, happiness, coping, relationships and self-worth) combine to the super dimension "Psychological Health". These super dimensions amalgamate to form the global AQoL-8D utility score.[270,271] The AQoL-8D has very high content, convergent and predictive validity,[272,273] and internal consistency.[270]

3.7.10.2 Severe Respiratory Insufficiency Questionnaire (SRI)

The SRI is a disease-specific multi-dimensional HRQoL questionnaire, designed for people with chronic respiratory failure, particularly those requiring home mechanical ventilation. It consists of seven sub-scales covering 49 items (Table 3-5), summarised to one summary scale (SRI-SS) between 0 and 100, with higher scores indicating a better HRQoL. Participants are provided with 49 statements related to various aspects of daily life, and are asked to rate "How did you feel last week?" for every statement on a five-point Likert scale, with answers from "completely untrue" to "always true". One sub-scale is dedicated to perceptions of breathlessness and sputum (e.g., "There is often mucus in my airways"), and will be used to assess change in respiratory symptoms over time.

Raw scores from all 49 questions are used to calculate the summary score, and at least half of the items per sub-scale must be answered. Developed in Germany, the SRI has good psychometric properties,[274] and is sensitive to change.[275-281] A study evaluating the English SRI version, produced by professional translation and back-translation, demonstrated higher psychometric properties than the original German SRI, plus high internal consistency, construct and concurrent validity.[282]

Sub-scale	Items	Question numbers
Respiratory complaints (SRI-RC)	8	2, 5, 12, 19, 22, 24, 25, 29
Physical functioning (SRI-PF)	6	1, 16, 32, 33, 41, 45
Attendant symptoms and sleep (SRI-AS)	7	6, 9, 11, 14, 17, 18, 42
Social relationships (SRI-SR)	6	7, 10, 21, 27, 43, 46
Anxiety (SRI-AX)	5	8, 13, 26, 28, 39
Psychological well-being (SRI-WB)	9	4, 20, 30, 34, 36, 38, 40, 44, 49
Social functioning (SRI-SF)	8	3, 15, 23, 31, 35, 37, 47, 48

Table 3-5: Severe Respiratory Insufficiency Questionnaire concepts

"Attendant" refers to participant.

3.7.10.3 REVISED AMYOTROPHIC LATERAL SCLEROSIS FUNCTIONAL RATING SCALE (ALSFRS-R)

The ALSFRS-R is a validated questionnaire-based scale that measures physical function during activities of daily living in people living with MND.[283] It is a revised version of the ALSFRS,[284] which disproportionately weighted limb and bulbar impairment above respiratory dysfunction. The ALSFRS-R incorporates three respiratory items (items 10 to 12) to replace the single breathing ability item on the original version, whilst retaining the three other concepts (fine motor, gross motor and bulbar function (items 1 to 3)). Each item on the ALSFRS-R refers to a particular functional activity or symptom, rated on a five-point scale from 4 (normal) to 0 (unable to perform). The ALSFRS-R correlates with an accepted QoL measure (the Sickness Impact Profile), has good internal consistency and construct validity.[283]

Individual items are summed to produce four sub-scores and an overall score (possible range of 0 and 48, higher scores indicate better function). The ASLFRS-R Slope was also

calculated at time of study enrolment ((48 minus ALSFRS-R summary score at Timepoint 0a) divided by months since symptom onset).[285]

3.7.11 Use of Prescribed Treatment

Participants in both the intervention and active control arms were instructed to document all performed exercise sessions in a diary. If no sessions were conducted, no record was to be made. Assessment of therapy usage was conducted at the 1-month, 2-month and 3-month study visits (Timepoints 1, 2 and 3b). Diaries were reviewed by an unblinded assessor; non-concordance with the prescribed treatment was identified and reasons explored. Non-performance of treatment was not a criterion for study withdrawal.

In addition, objective usage was collected for participants assigned to the intervention arm via a custom-made device ("LVR counter") attached to their LVR kit (Section 4.5).

3.7.12 Side Effects of Therapy

Participants were instructed to document any problems with their treatment, for example chest soreness or muscle discomfort, light-headedness, dizziness or shortness of breath in their self-report diaries. These were checked by the unblinded assessor at each study visit, and escalated to the VRSS physiotherapist or study's adverse event contact person (a nominated VRSS Respiratory and Sleep Physician) if necessary. The unblinded assessor added any side effects or free-text comments to the de-identified electronic version of the participant's self-report diary.

3.7.13 Self-reported Hospitalisation Rate

At each study visit, the unblinded assessor asked about *any* hospital inpatient, emergency department or primary-care practitioner visits since the last timepoint. Participants were also questioned about "chest infection" symptoms and subsequent changes to medication, therapy and/or NIV use. Dates and the clinical issue were noted in the de-identified electronic version of the participant's self-report diary.

3.8 STATISTICAL ANALYSES

3.8.1 DATA MANAGEMENT

Data was collected by the research team at each timepoint in digital format (e.g., Spike2 data files, Hyp'Air Compact Plus® data, Omega® proprietary data files), and de-identified at source using a unique patient identification number (e.g. AH*xyz*00001). Data was re-identifiable only with the use of a "key" held by the principal researcher, in a password-protected spreadsheet. Re-identification of individual participant data was required for quality assurance of data entry and to enable communication of relevant results to each participant's clinical team.

De-identified raw signals (LIC, VC, C_{rs}, PCF, PCF_{LIC}) and respiratory function test outputs (static lung volumes, MIP, MEP, SNIP) were processed by assessors blinded to participant treatment group and values recorded in paper format.

All de-identified data was entered into a password-protected 256-bit encrypted web-based electronic database, with unique login and password combination (Adept Research, Helmut Design Pty Ltd, Melbourne, Australia). This secure-data hosting service with offsite backup also generated the unique participant numbers, and allowed different permissions to be set for data collectors to prevent unblinding (i.e., unblinded or blinded access). De-identified data was exported from the Adept Research database in .csv format for data analysis in statistical software (Stata®/IC 15.1 for Mac, StataCorp LLC, Texas, USA). Only researchers named on the ethics submission had access to the complete data set.

3.8.2 POWER CALCULATIONS

At the time the study's protocol was developed, there was little published data reporting change in MIC or LIC over time with regular LVR. A mean change of 100 ± 400 mL over a median follow-up period of 45 months was reported in a cohort study of 22 participants with DMD prescribed LVR twice-daily (baseline FVC = 1.0 $\pm$ 0.7 L).[137] In

comparison, a three-month prospective uncontrolled feasibility study of participants prescribed LVR up to four times daily observed a group mean change of 154 mL in 19 people with heterogeneous NMD. Within the eight people diagnosed with MND, a change in MIC of 188 mL was reported (95% CI = -71 to +447 mL, or standard deviation (SD) ± 310 mL calculated by converting the published data).[220]

Therefore, to detect a between-treatment difference of mean change in LIC of 150 mL over three months with a SD of 310 mL, assuming 80% power and a two-sided statistical significance level of 0.05, it was calculated that 36 participants per group (total = 72) would be required to complete this research study. To allow for a 15% participant withdrawal rate, a total of 83 participants were sought for recruitment and randomisation.

3.8.3 ANALYSIS PLAN

Null hypotheses of each component of this research project are detailed within the corresponding results chapter. Statistical analyses were performed using Stata® statistical software (Stata®/IC 15.1 for Mac, StataCorp LLC, Texas, USA). Results are presented as: mean ± SD; median (interquartile range (IQR) = lower quartile – upper quartile "*x – y*"); mean (95% confidence interval (CI) = "*x, y*") or frequencies and percentages as appropriate. Change over time data are presented as group mean difference (95% confidence interval).

For the project as a whole, disease type was defined *a priori* and categorised as either "MND" (participants with the rapidly-progressive ALS form of MND), or "Other" (all other NMDs, including restrictive chest wall disease).

In Chapter 6, RTI history was dichotomised as "RTI" (RTI reported in prior 12 months) or "No RTI" (no RTI in prior 12 months). For Part 2, the prospective pre-post intervention study investigating the immediate effects of a single-session of LVR (Chapter 7), change over time (Timepoint 0b minus 0a) was examined for the group as a whole and then by disease type. To investigate the role of regular LVR (Part 3: Chapter 8), participants were grouped by their allocated treatment (LVR or Breathing

exercises) and intention-to-treat analyses conducted. The study's primary analysis was the between-group difference of the mean change in LIC over three months (i.e., between-group comparison of Delta LIC, where Delta = Timepoint 3a minus 0a). Secondary analyses by disease type were planned *a priori*. Rate of change in respiratory function at monthly intervals were considered exploratory analyses.

Between-group comparisons were performed using Student's independent two-sample *t*-test for the comparison of means or Fisher's exact test for proportions. For data that was not normally distributed or non-parametric, between-group comparisons were conducted using the Wilcoxon rank-sum test (also known as the Mann-Whitney two-sample *U*-statistic). *P*-values <0.05 were considered statistically significant.

Within-group change over time was assessed using paired *t*-tests (two timepoints). Linear mixed models (restricted maximal likelihood option) were employed when measures were performed at more than two timepoints *or* sub-group analyses by treatment group (LVR or Control) or disease type (MND or Other NMD) were planned. If the result of a model was statistically significant or if interaction effects were present, post-hoc comparisons were conducted to explore main effects (effect of time via pairwise comparisons via paired *t*-tests; effect of disease or treatment via two-sample *t*-test at timepoint). For treatment and time interactions, the magnitude of change across time was compared (e.g. two-sample *t*-test between-group comparison of mean change ΔTime; e.g. Timepoint 0b minus 0a, Timepoint 3a minus 0a, or Timepoint 3b minus 3a).

Exploratory analyses examining the relationships between variables (selected *a priori*) were conducted by univariate linear regression analyses (Pearson's correlation coefficient, r). Multivariate regression models were built manually to determine the influence of explanatory variables on the response variables, using outcome measures that were found to be significant on univariate analysis (p<0.100). Logistic regression modelling was also undertaken to explore respiratory variables associated with a prior RTI (Chapter 6). Receiver operating characteristic (ROC) curves were constructed to

evaluate the sensitivity and specificity of published cut-off values (VC <1.1 L and PCF <160 L/min[168]) to predict (i.e., identify) which participants had a past history of RTI.

For analysis of therapy usage over the study duration self-reported diary data were expressed as i) average number of sessions performed per day (average sessions = total number of sessions reported over the study duration divided by study duration) and ii) the proportion of days none, one and at least two sessions were conducted (Zero/day (%), Once/day (%), Two plus/day (%)). Lung volume recruitment usage obtained from the LVR counter was analysed as i) average LVR sessions (total number of LVR sessions recorded over the study duration, divided by study duration), ii) average minutes of daily therapy (total minutes recorded divided by study duration), and iii) average minutes performed per session (total minutes divided by number of LVR therapy sessions).

Agreement between the LVR counter and self-reported use was evaluated using the concordance correlation coefficient (CCC) and Bland and Altman's limits of agreement. Pearson's correlation coefficient and univariate regression analyses were performed to investigate the relationship between changes in respiratory function over the three-months (i.e., primary and secondary outcome measures) and dose.

4 METHODS: EQUIPMENT & MEASUREMENT PROCEDURES

4.1 LABORATORY-GRADE SYSTEM

4.1.1 HEATED PNEUMOTACHOMETER

All pneumotachometer and associated equipment were from the Hans Rudolph™ company (Hans Rudolph, inc., Kansas, USA). A paediatric pneumotachometer with low dead space volume (13.87 mL) and a linear response guaranteed over flow rates from 0 to 160 L/min was used because of the expected respiratory impairment in the study population (Model 3700A). The pneumotachometer was calibrated against a three-litre volume syringe prior to every testing session, and demonstrated a linear response beyond the guaranteed range. The pneumotachometer was connected to a heater control unit set at 37 degrees Celsius (°C). A Pneumotach amplifier and differential pressure transducer (PA-1 Series 1110) measured the pneumotachometer differential pressure signal and converted it into an analogue electrical value which was amplified and demodulated prior to sending to a data acquisition system. The transducer had a second sensor for mouth pressure.

The default range of the analogue output was -5 to +5 volts. Preparatory testing with a three-litre syringe identified clipping of bi-directional flow at rates greater than 150 L/min, hence the amplifier jumpers were adjusted to increase the output range (Figure 4-1).

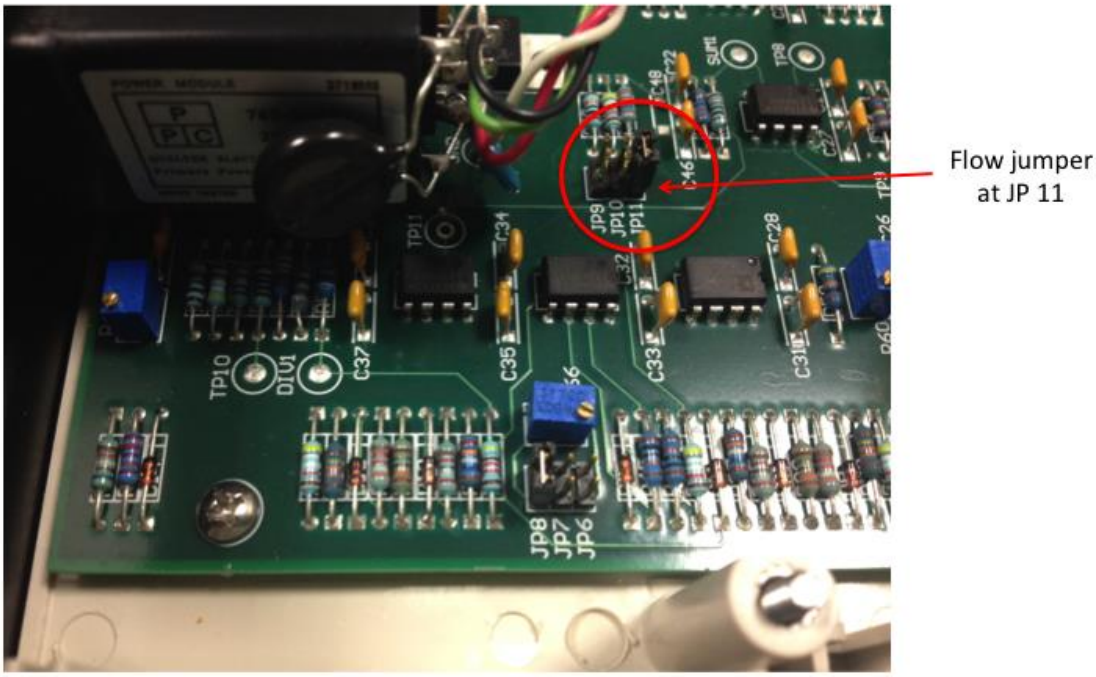

Figure 4-1: Close up image of the Hans Rudolph PA-1 amplifier circuit board

Adjustment of the electrical flow jumper (black case) to position JP11 (output range -/+ 1 volts) was undertaken as per the manufacturer's Operation Instructions. Clipping of airflow occurred at rates exceeding 720 L/min and was deemed optimal for the planned experiment. The jumper for pressure measurement was left in the default position of JP2 (output voltage range -/+ 5 volts). Clipping of the pressure signal occurred beyond the anticipated range required for this study (above 73 cmH_2O).

4.1.2 PRESSURE AND FLOW SIGNAL RECORDING

Bi-directional flow and pressure outputs from the Pneumotach Amplifier (PA-1) were recorded continuously by a multi-channel, analogue-to-digital data acquisition system recording at a sampling rate of 100 Hz (CED Micro 1401 hardware and Spike2 (version 7) software, Cambridge Electronic Design Limited, Cambridge, England). Two input waveform channels received signals from the testing circuit; Channel 1 (Ch1) received the raw flow signal (volts) and Channel 2 (Ch2) the pressure signal representing P_{mo}.

Prior to testing, the unheated pneumotachometer was flow-calibrated using a three-litre syringe. A series of 36 syringe strokes, all of equal volume but at various flow rates covering the anticipated range to be sampled during participant testing, were recorded. A published Spike2 script for calibration of a pneumotachometer (version 7,

PTCal07) converted this raw flow signal (Ch1, volts) to flow (virtual channel v1, measured in L/s) under ambient (ATP) conditions.

A second procedure calibrated the pressure signal (P_{mo}) using a two-point calibration method. A pressure signal recording (Ch2) was generated manually using a 5 mL syringe, and compared to simultaneous measurement of true pressure using a hand-held digital manometer. Calibration was achieved using the in-built Spike2 calibration options.

4.1.3 DERIVATION OF VOLUME SIGNAL

Inspired and expired volume was obtained by real-time numerical integration of the flow signal using a custom-written data sampling script in Spike2 software. This script comprised two components: i) application of a BTPS-correction factor to convert the calibrated flow channel (v1) from ATP conditions to BTPS conditions within the lungs (BTPS-corrected flow (Ch4)), and ii) mathematical integration of BTPS-corrected flow to BTPS-corrected volume (Ch3) (Appendices 11.1.1, 11.1.2 and 11.1.3).

4.2 COMMERCIAL SYSTEM

To be able to conduct Timepoints 1 and 2 in participants' homes (Figure 4-2), static lung volume measurements were performed using the multiple-breath nitrogen washout technique,[47,254] (Hyp'Air Compact Plus® Portable PFT System; Medisoft, Sorinnes, Belgium). In light of the anticipated small tidal volumes and flows in this population, equipment was selected to minimise dead space and circuit resistance. A paediatric pneumotachometer was used for all tests (paediatric Lilly-type heated pneumotachometer dead space 20 mL, resistance 0.4 $cmH_2O/L/sec$), and a gas-impermeable reservoir bag rather than a demand valve system was selected for nitrogen washout testing. Dead space of the standard mouthpiece was 80 mL, or 135 mL when an oro-nasal mask was used. Testing was conducted on a biological control participant using the two interfaces to ensure measurement repeatability regardless of which interface was used.

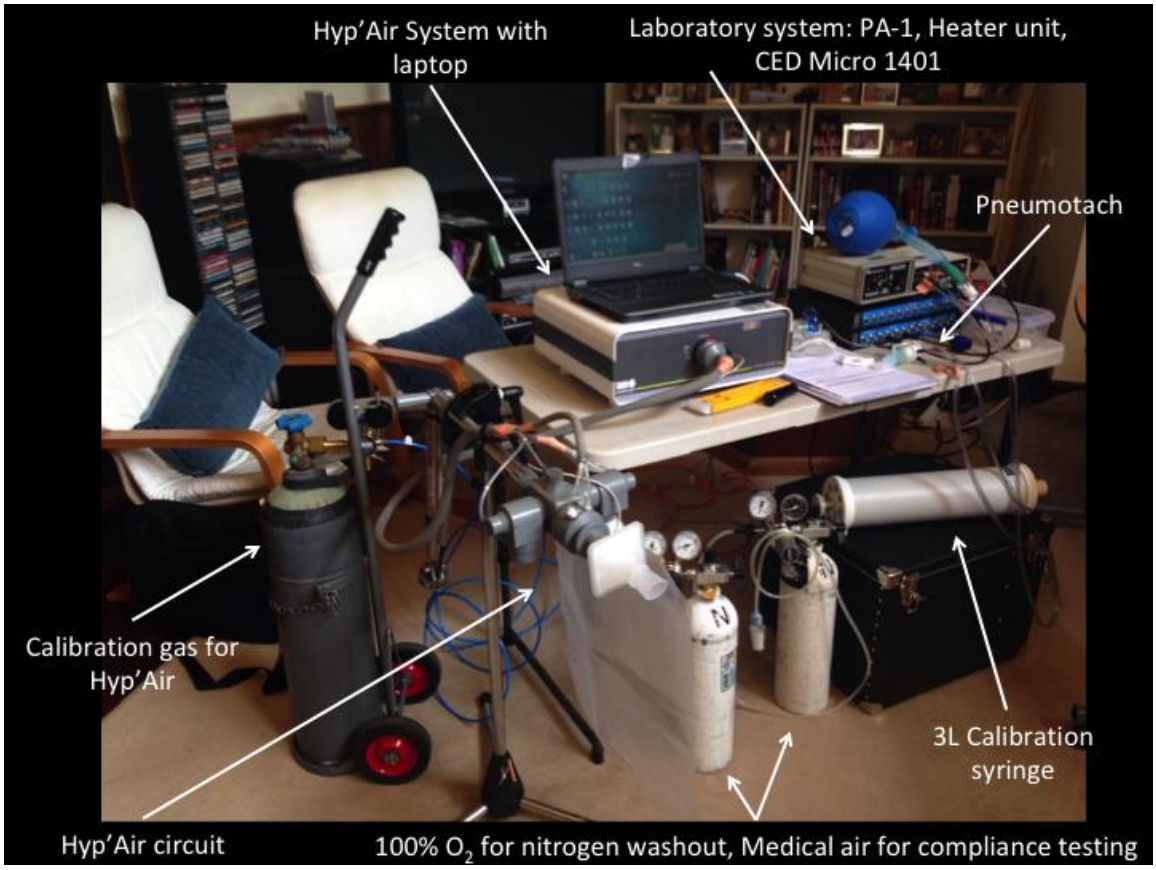

Figure 4-2: In-home collection of respiratory function measures

Set-up illustrates the commercially-available portable pulmonary function testing system on the left (Hyp'Air Compact Plus® Portable PFT System). The system comprised the Hyp'Air Compact Plus® device, circuit and pneumotachometer, laptop personal computer, two gas cylinders and regulators (calibration gas and 100% medical oxygen (O_2)), associated tubing and communication cable, articulated arm/stand, and calibration syringe). The laboratory-grade system (Hans Rudolph™ Pneumotachometer Model 3700A, Pneumotachometer Heater Control unit, Pneumotach Amplifier 1 (PA-1) Series 1110, CED Micro 1401 data acquisition system) is positioned on the right.

4.3 CIRCUIT DESIGN

Numerous circuit configurations were required to perform the multiple outcome measures of respiratory function. The base circuit, used to measure VC (Figure 4-3) and PCF (Figure 4-4), comprised the participant interface, pressure line connector and calibrated heated pneumotachograph.

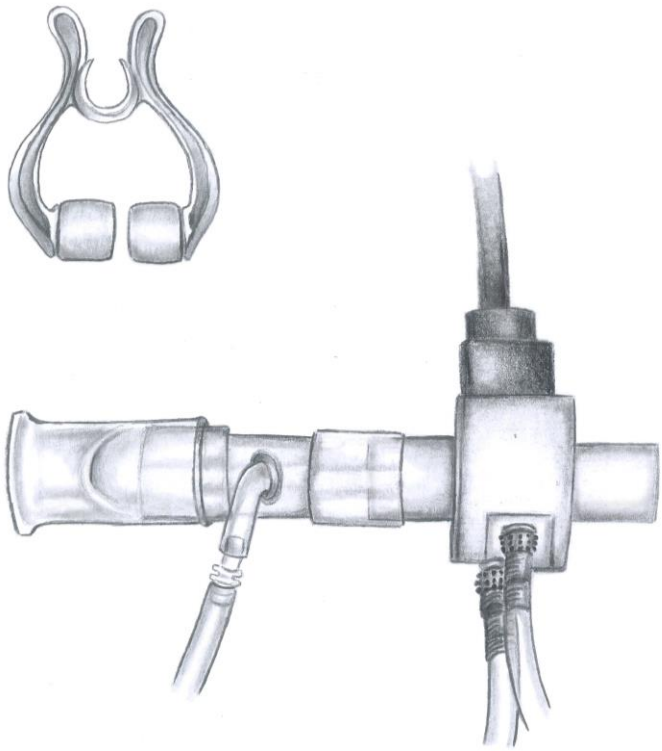

Figure 4-3: Base circuit, as used for measuring VC

VC = vital capacity
Components from left to right: mouthpiece, pressure line connector *(approximating mouth pressure, P_{mo})*, pneumotachometer and heater shell *(determining flow and volume; Hans Rudolph™ Model 3700A).*
The heating wire can be seen protruding from the top (connects to *Hans Rudolph™ Pneumotachometer Heater Control unit*), whilst the two pressure lines that derive differential pressure and hence flow arise from the bottom and attach to the *Hans Rudolph™ Pneumotach Amplifier 1 (PA-1) Series 1110.* The P_{mo} pressure line attached to a second pressure transducer input on the amplifier.

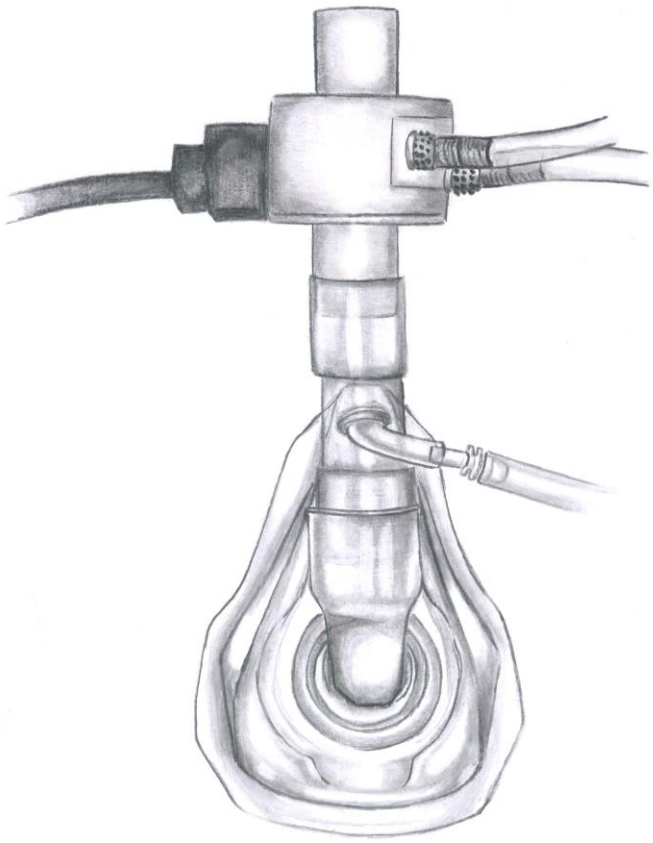

Figure 4-4: Base circuit, as used for measuring PCF

PCF = peak cough flow
Components from top to bottom: pneumotachometer and heater shell (*determining flow and volume)*, pressure line connector *(approximating mouth pressure, P_{mo})* and non-vented oro-nasal face mask.

A three-port tap connector was added to this for LIC (Figure 4-5), PCF_{LIC} (Figure 4-6) and C_{rs} testing (Figure 4-7). The participant interface, pressure line connector and pneumotachometer connected in series to the first port, which was always open (participant limb). The second port of the tap connector, distal to the pneumotachometer and participant, opened to the atmosphere (spontaneous limb). The third port (inflation limb) connected to either i) the LVR kit, or ii) to a cylinder of compressed medical air with an adjustable flow regulator via a length of narrow bore tubing. A tap controlled the second and third ports, such that only one of these could be open and connect with the participant limb at any given time. Opening the tap connected the participant to the atmosphere and allowed spontaneous inhalation and exhalation whilst occluding flow from the inflation limb. When the tap was closed, the second port became occluded and the inflation limb opened, allowing i) LVR or ii) constant flow of medical air for C_{rs} measurements.

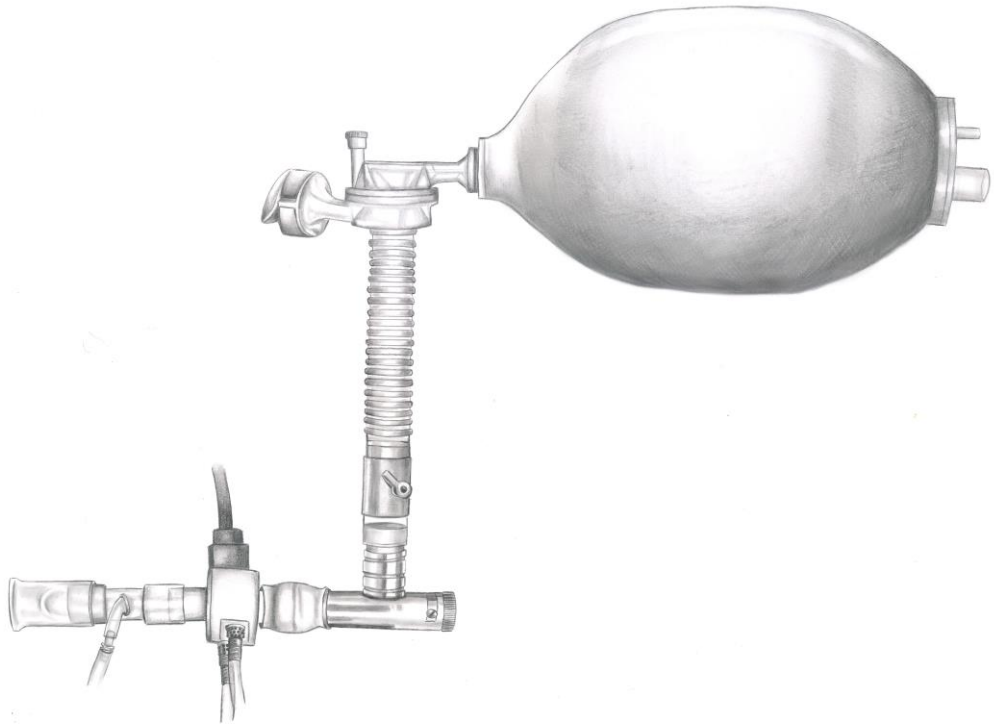

Figure 4-5: Customised circuit, as used for measuring LIC

LIC = lung insufflation capacity
Components from left to right: mouthpiece, pressure line connector *(approximating mouth pressure, P_{mo})*, pneumotachometer and heater shell *(determining flow and volume)*, three-port tap connector and lung volume recruitment (LVR) kit.
The right-angled tap connector opened to the participant (via pneumotachometer) and LVR kit (via inflation limb). An additional port (outlet not visible) opened to the atmosphere and was controlled by twisting the tap's end.

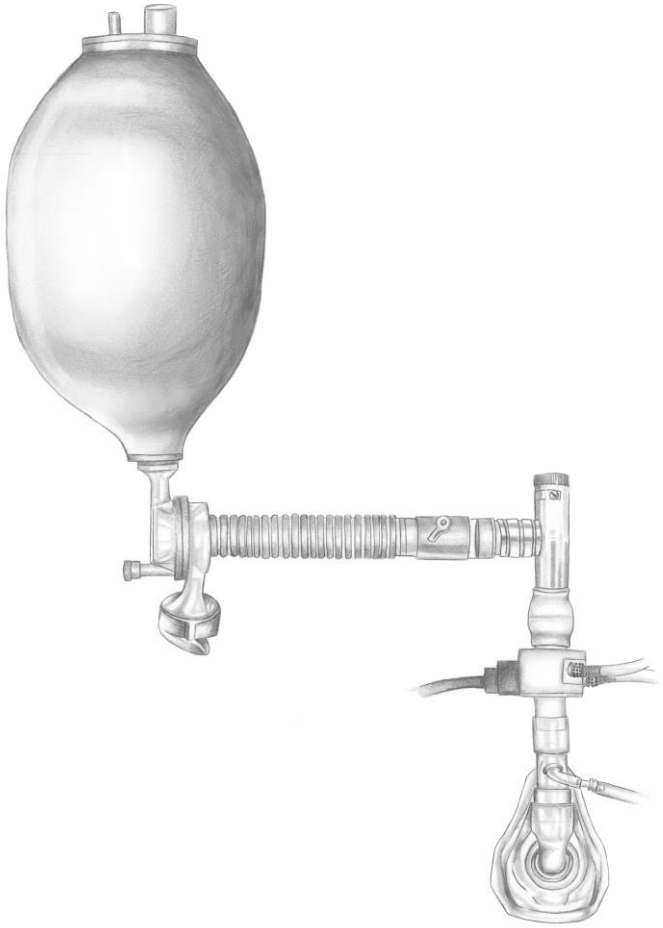

Figure 4-6: Customised circuit, as used for measuring PCF_{LIC}

PCF_{LIC} = peak cough flow from lung insufflation capacity
Components from top-left to bottom-right: lung volume recruitment (LVR) kit, three-port tap connector, pneumotachometer and heater shell (*determining flow and volume)*, pressure line connector *(approximating mouth pressure, P_{mo})* and non-vented oro-nasal face mask.

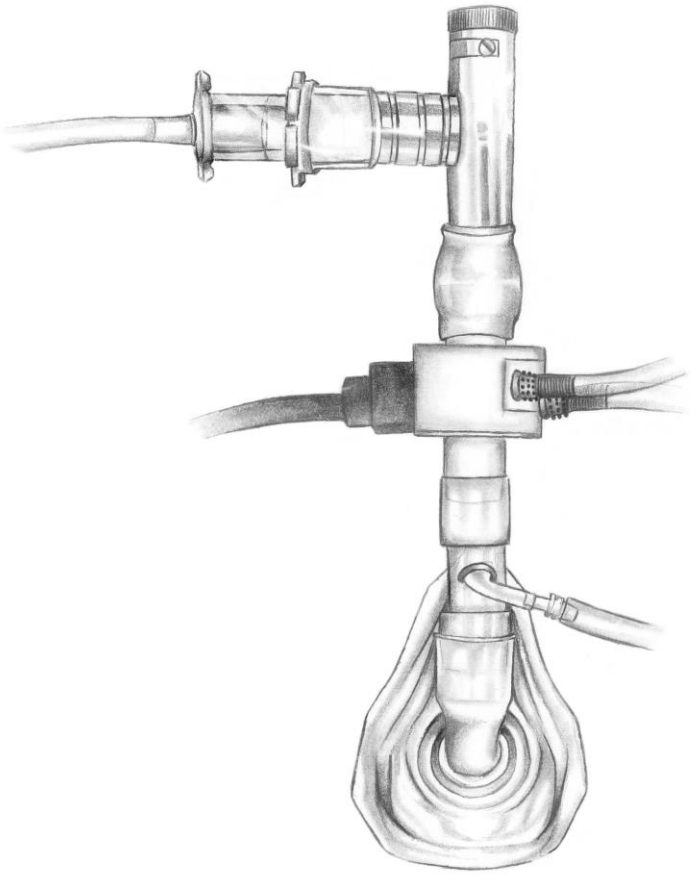

Figure 4-7: Customised circuit, as used for measuring C_{rs}

C_{rs} = respiratory system compliance
Components from top to bottom: three-port tap connector, narrow bore tubing and connector attaching to inflation limb (from cylinder of compressed medical air, not shown), pneumotachometer and heater shell *(determining flow and volume)*, pressure line connector *(approximating mouth pressure, P_{mo})*, and non-vented oro-nasal mask.

Given three of these five circuit configurations require a right-angled tap connector, two perform measurements with the pneumotachometer under a pressure load (LIC and PCF_{LIC}), and at least three use an oro-nasal mask rather than mouthpiece and nose clip, experiments were conducted to determine whether these factors altered the pneumotachometer accuracy (Sections 4.3.1 and 4.3.2).

4.3.1 EXPERIMENT: EFFECT OF CIRCUIT DESIGN ON PNEUMOTACHOMETER

4.3.1.1 BACKGROUND AND AIMS

A differential pneumotachometer works on the principle that the pressure differential across the resistive screens is proportional to gas flow, providing airflow is laminar. Turbulent gas flow upstream or downstream of the pneumotachometer may disrupt laminar flow and thus flow and volume measurements.

The aim of this experiment was therefore to determine the effect of each circuit design on the measured airflow, specifically i) whether the volume measured by the pneumotachometer remained constant regardless of an additional downstream connector, ii) circuit geometry and iii) interface.

4.3.1.2 METHOD

To evaluate the effects of circuitry and geometry on the calibrated pneumotachometer, a bench-test experiment of four conditions was conducted:

1. pneumotachometer (base state)
2. pressure connector, pneumotachometer
3. pressure connector, pneumotachometer, straight three-port tap
4. pressure connector, pneumotachometer, right-angled three-port tap

Calibration of the pneumotachometer as described in Section 4.1.2, without any additional connectors or interface constituted the base state (Condition 1). A three-litre volume syringe was attached in turn to each test condition set-up. A sequence of 36 inward and outward strokes was performed, and the resultant volume analysed. The pneumotachometer heater remained off for all testing (hence ATP conditions) and the sampling script used contained no BTPS-correction factors.

To evaluate the effect of geometry on the calibrated pneumotachometer under participant testing conditions, a biological control participant (PR) performed FVC manoeuvres through Conditions 3 and 4, via a mouthpiece with nose clip in situ. For

this part of the experiment, the pneumotachometer heater was turned on and a sampling script containing BTPS-correction factors used. The FVC results obtained were compared.

To evaluate the effect of interface on the calibrated pneumotachometer under participant testing conditions, a biological control participant (NS) performed FVC manoeuvres through Condition 2, using two different interfaces:

5. mouthpiece and nose clip, pressure connector, pneumotachometer
6. oro-nasal mask, pressure connector, pneumotachometer

4.3.1.3 RESULTS

Mean volumes recorded under each test condition are presented in Table 4-1. Ambient air temperature and relative humidity at the time of testing was 20 °C and 45% respectively.

Condition	Measured Inspiratory Volume (L)*	Measured Expiratory Volume (L)*	Biological controls FVC (L)
1. Base state (PnTc)	2.997	3.025	-
2. Pressure connector + PnTc	3.006	2.996	-
3. Pressure connector + PnTc + tap	2.998	3.005	4.270
4. Pressure connector + PnTc + 90° tap	3.004	2.988	4.290
5. MP, pressure connector + PnTc	-	-	3.850
6. Mask, pressure connector + PnTc	-	-	3.837

Table 4-1: Circuit design experiments

The first two columns (*) refer to the bench-test, performed using a 3-litre (L) syringe. The shaded column of results were obtained in biological controls.
PnTc = pneumotachometer, MP = mouthpiece, FVC = forced vital capacity.

For the bench-test experiment evaluating circuitry and geometry, measured volume ranged from 2.988 L (syringe volume minus 12 mL) to 3.025 L (syringe volume plus 25 mL), representing a maximum measurement error of 0.8 % at 3L, regardless of the circuit used.

For the biological control experiments, the use of a straight versus right-angled circuit design resulted in a mean difference of 20mL (0.5% of measurement). The use of a mouthpiece and nose clip versus oro-nasal mask resulted in a mean difference of 13mL (0.3% of measurement).

4.3.1.4 CONCLUSION

In a bench-test environment, the addition of connectors and taps to a calibrated pneumotachometer did not introduce measurement error that was clinically meaningful. Similarly, the geometry of the taps did not appear to affect the airflow and hence volume measured by the pneumotachometer during bench-test; there was no clinically meaningful difference between FVC values recorded within-participants, despite variations in the geometry of the testing circuit or interface used. The absolute and percentage differences observed were both very small, and well within normal intra-individual variability for this test.

These findings suggest that the three variables examined herein (configuration, geometry and interface) did not alter gas airflow behaviour at the pneumotachometer by a clinically important amount. The five circuit designs used for the measurement of respiratory function outcomes in this research study were therefore deemed valid for measurement purposes.

4.3.2 EXPERIMENT: EFFECT OF LOAD ON PNEUMOTACHOMETER

4.3.2.1 BACKGROUND AND AIMS

The aim of this experiment was to determine the performance of the pneumotachometer under normal conditions (i.e., unimpeded inspiration and expiration) and when the system is under a pressure load or subject to compressive force (e.g., positive pressure delivered via the LVR kit).

4.3.2.2 METHOD

A bench-test experiment of three conditions was conducted:

1. Unresisted airflow (base state)
2. Resisted inward airflow
3. Positive pressure (LVR) inflation

The laboratory-grade system was setup and calibrated as described above (Section 4.1.2). The pneumotachometer heater remained off for all testing. Flow, volume and pressure recorded by the pneumotachometer for each inward and outward stroke was measured for each of the three test conditions.

The experimental set-up for Conditions 1 and 2 were similar. A three-litre volume syringe was connected to the pneumotachometer and pressure connector (in series), with the distal outlet open. For Condition 1, a sequence of 36 inward and outward strokes was performed. For Condition 2, this sequence was repeated, however resistance was applied during inward airflow by partially occluding the outlet. Outward airflow remained unimpeded.

To test the response of the pneumotachometer under pressurised airflow (Condition 3), the three-litre syringe was connected in series to the pressure connector, pneumotachometer, and three-port tap connector. A LVR kit was attached to the third port (inflation limb) (Figure 4-8). This circuit was the same design as used for the measurement of LIC and PCF_{LIC}, minus the participant interface (compare with Figure

4-5 and Figure 4-6). Testing commenced with the syringe empty and was inflated to its full three-litre capacity by compressing the LVR kit, replicating airflow passing through the pneumotachometer under a pressure load in accordance with participant testing. The three-port tap was then operated so that the syringe and circuit opened to the atmosphere, and the full syringe emptied.

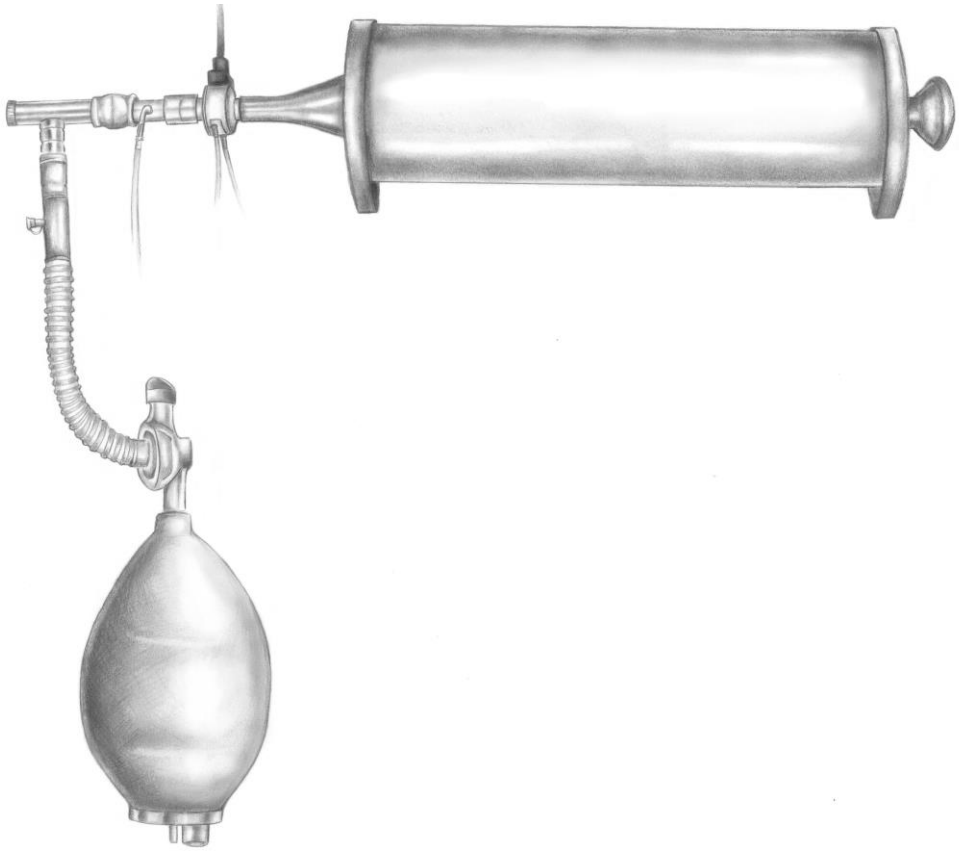

Figure 4-8: Set up for testing Condition 3: Positive pressure load on pneumotachometer

Components clockwise from bottom to top right: lung volume recruitment (LVR) kit, three-port tap connector, pressure line connector *(measuring pressure)*, pneumotachometer and heater shell *(determining flow and volume)*, and three-litre calibration syringe.

4.3.2.3 RESULTS

Mean volume, flow and pressure recorded under each test condition are presented in Table 4-2.

Condition	Measured inward Volume (L)*	Measured outward Volume (L)*	Peak inward Flow (L/s)	Peak outward Flow (L/s)	Peak inward Pressure (cmH_2O)	Peak outward Pressure (cmH_2O)
1. Unresisted airflow	2.982	2.960	2.32	2.59	-0.58	-1.41
2. Resisted inward airflow	2.962	2.946	1.23	3.63	34.53	-2.82
3. LVR Inflation	3.065	3.098	2.99	4.20	55.70	-1.43

Table 4-2: Pressure load experiment

* = performed using a 3 litre (L) syringe

Measured inward volume for unresisted airflow (Condition 1) and resisted inward airflow (Condition 2) were within 20 mL of each other (relative percentage error = 1.3%). Similarly, measured outward volumes differed by 14 mL, with the largest of these differing from the expected syringe volume by 54 mL (relative percentage error = 1.8%).

The mean inward and outward volumes measured when the pneumotachometer was under a pressure load (Condition 3) were both greater than the known three-litre volume (syringe volume plus 65 mL and 98 mL respectively). The magnitude of relative error (2.2% for inspiratory measurements and 3.3% for expiratory measurements) is similar to the <3% relative error of the commercially-available pneumotachometer used in this study (Hyp'Air Compact Plus® Portable PFT System).

4.3.2.4 CONCLUSION

The measurement error observed in the volume signal obtained under conditions simulating spontaneous inspiration and expiration, and pressurised airflow simulating LVR was within a clinically acceptable range. This suggests that the level of back pressure anticipated during participant testing will not greatly affect the ability of the pneumotachometer to determine flow and hence volume. The equipment employed for respiratory function testing in this research study was therefore considered valid.

4.4 SIGNAL ANALYSES

Raw flow, volume and pressure traces were analysed to derive LIC, VC, PCF, PCF_{LIC} and C_{rs}. The criteria used are explained below for all except $C_{rs.}$ As this latter outcome measure is not widely used in participants with NMD, a dedicated chapter pertaining to the measurement, analysis and scoring rules for C_{rs} is provided (Chapter 5).

4.4.1 LUNG INSUFFLATION CAPACITY (LIC)

The LIC was calculated for each manoeuvre from the volume signal. Cursors were positioned manually i) at the uppermost point achieved after delivery of consecutive positive pressure insufflations (maximum tolerable insufflation capacity / maximal inflation volume), and ii) at the lowermost point recorded on the subsequent exhalation (Figure 4-9). The corresponding flow and pressure signals were cross-referenced to ensure that both the assisted inflation and expiration were technically acceptable. An assisted inflation trace was considered unacceptable if there was resistance to pressure and flow traces, such as during reflexive glottic closure, or leak. Exhalation to RV was inferred if expiratory volume was more negative than tidal breathing, and was determined at the point when expiratory flow returned to zero. The expiratory component was assessed to ensure small spontaneous inspiratory efforts were not made, especially approaching the end of expiration, which may have artificially increased exhaled volume. If pressure or flow signals suggested an inspiratory effort was made, the exhaled volume immediately prior to this was taken as the end point (RV) (Figure 4-10).

Lung insufflation capacity was taken as the volume between the two cursors, and the largest, technically acceptable LIC value was used in analysis.

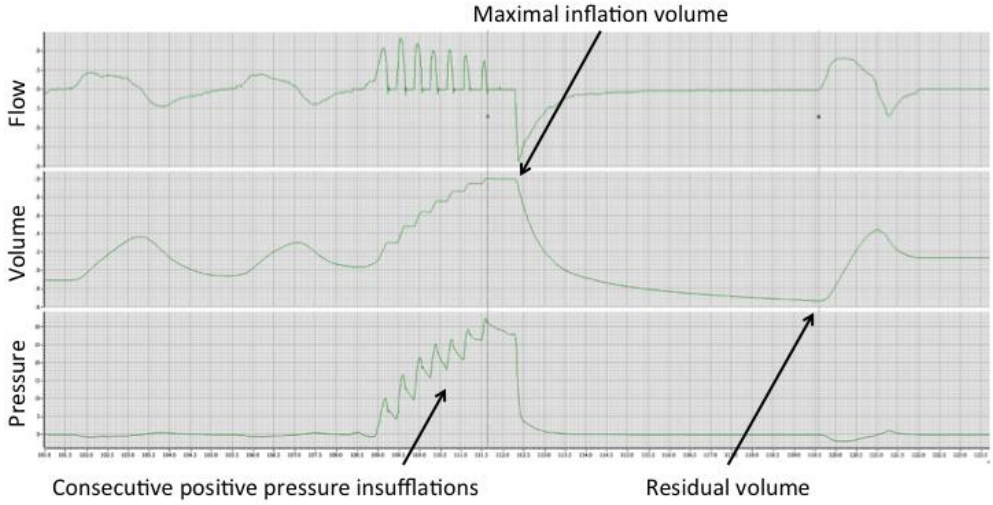

Figure 4-9: Measurement of LIC

Lung insufflation capacity (LIC) was taken as the exhaled volume (in litres) following consecutive insufflation to the participant's maximum tolerable insufflation capacity (or maximal inflation volume to residual volume).

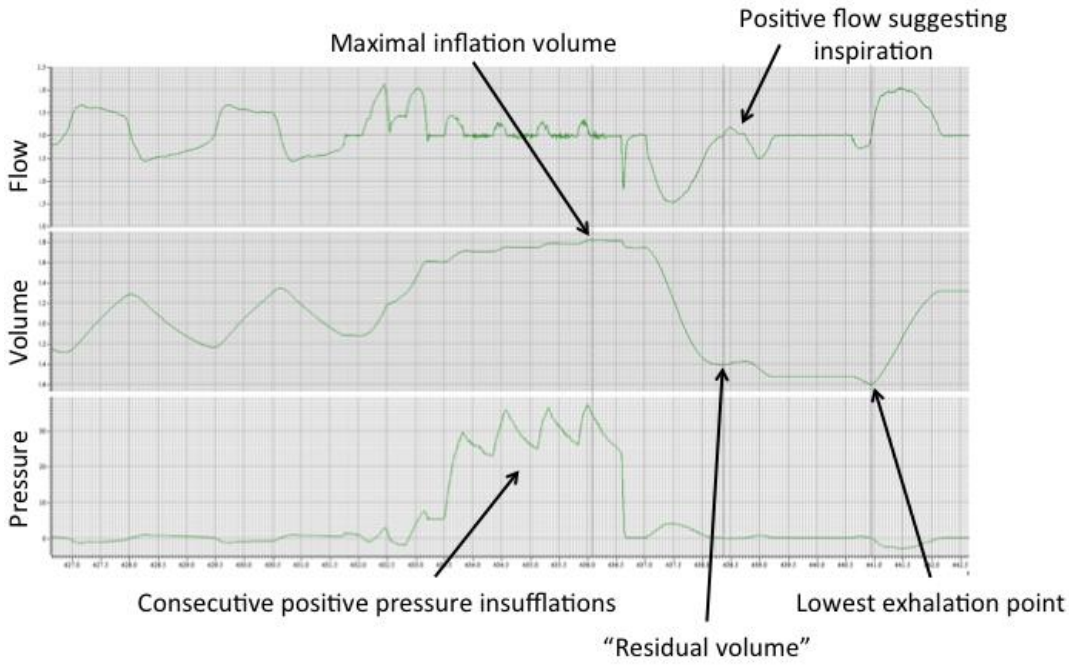

Figure 4-10: Measurement of LIC, in participant with inspiratory effort

Lung insufflation capacity (LIC) was taken as the exhaled volume (in litres) following consecutive insufflation to the participant's maximum tolerable assisted inflation capacity. Note small inspiratory efforts towards end-expiration; residual volume taken prior to these (maximal inflation volume to residual volume).

4.4.2 VITAL CAPACITY (VC)

Vital capacity was calculated for each manoeuvre from the volume signal. Cursors were positioned manually i) at the uppermost point achieved after a single spontaneous, inspiration (maximum inspiratory capacity, IC), and ii) at the lowermost point recorded on the subsequent forced exhalation (Figure 4-11). The corresponding flow and pressure signals were cross-referenced to ensure that both the spontaneous inspiration and expiration were technically acceptable. Inspiration was assessed to ensure the participant had not augmented IC by stacking multiple inspiratory efforts (i.e., spontaneous breath-stacking). Exhalation to RV was inferred as per for the LIC signal analysis.

Vital capacity was calculated as the volume between these two cursors with the largest, technically acceptable value used in analysis.

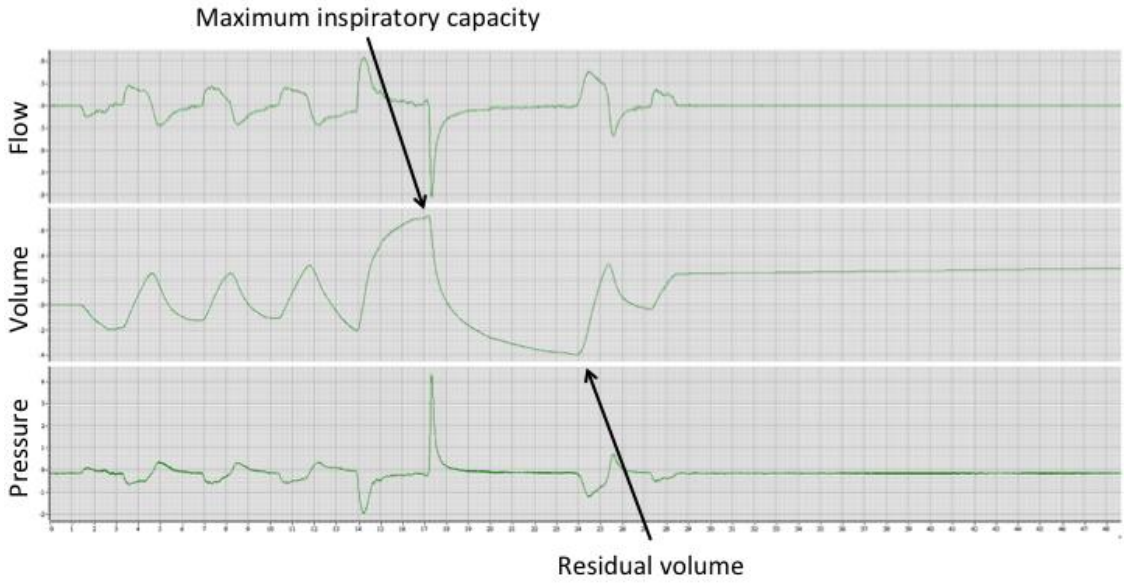

Figure 4-11: Measurement of VC

Vital capacity (VC) was taken as the exhaled volume (in litres) following maximal inspiration (maximum inspiratory capacity to residual volume).

4.4.3 UNASSISTED PEAK COUGH FLOW (PCF)

The PCF was calculated for each manoeuvre from the flow signal. A horizontal cursor was positioned manually at the most negative point immediately following a cough manoeuvre (maximum peak expiratory flow associated with a cough) (Figure 4-12). This was typically easily identifiable due to the rapid velocity of airflow creating a clear expiratory peak or spike. Generally, the PCF was the first spike, however if a subsequent spike within the same expiratory phase was greater (i.e., no inspiratory effort had occurred between the spikes), then that was recorded as the PCF.

Achieving maximal IC was not a requirement of the PCF manoeuvre; participants were instructed to produce "their biggest, strongest cough". However, the flow and corresponding volume signals were cross-referenced to ensure that the pre-cough inspiration was greater than tidal volume breathing, had not been augmented by spontaneous breath-stacking, and was effortful. Similarly the pressure and flow signals were used as an estimate of participant effort.

The flow rate reached at the tip of the expiratory peak was recorded as PCF, and the largest, technically acceptable value used in analysis.

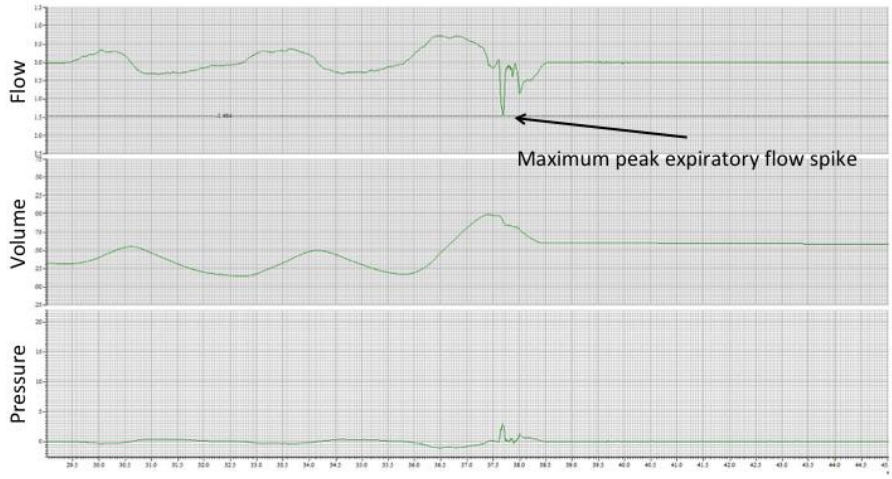

Figure 4-12: Measurement of PCF

Peak cough flow (PCF) was taken as the maximum peak expiratory flow (in litres per second, later converted to litres per minute) following a volitional cough. Participants were instructed to produce "their biggest, stongest cough".

4.4.4 PEAK COUGH FLOW FROM LUNG INSUFFLATION CAPACITY (PCF_{LIC})

The PCF_{LIC} was calculated for each manoeuvre from the flow signal. As per signal analysis for PCF, a horizontal cursor was positioned manually at the most negative point immediately following a cough manoeuvre, following the same identification procedures. Distinguishing this from unassisted PCF, this cough was performed from maximal tolerable insufflation capacity (i.e., immediately succeeding maximal inflation using a LVR kit). The corresponding volume and pressure signals were cross-referenced to ensure that the pre-cough assisted inflation was technically acceptable.

The flow rate reached at the tip of the expiratory peak (Figure 4-13) was recorded as PCF_{LIC}, and the largest, technically acceptable value used in analysis.

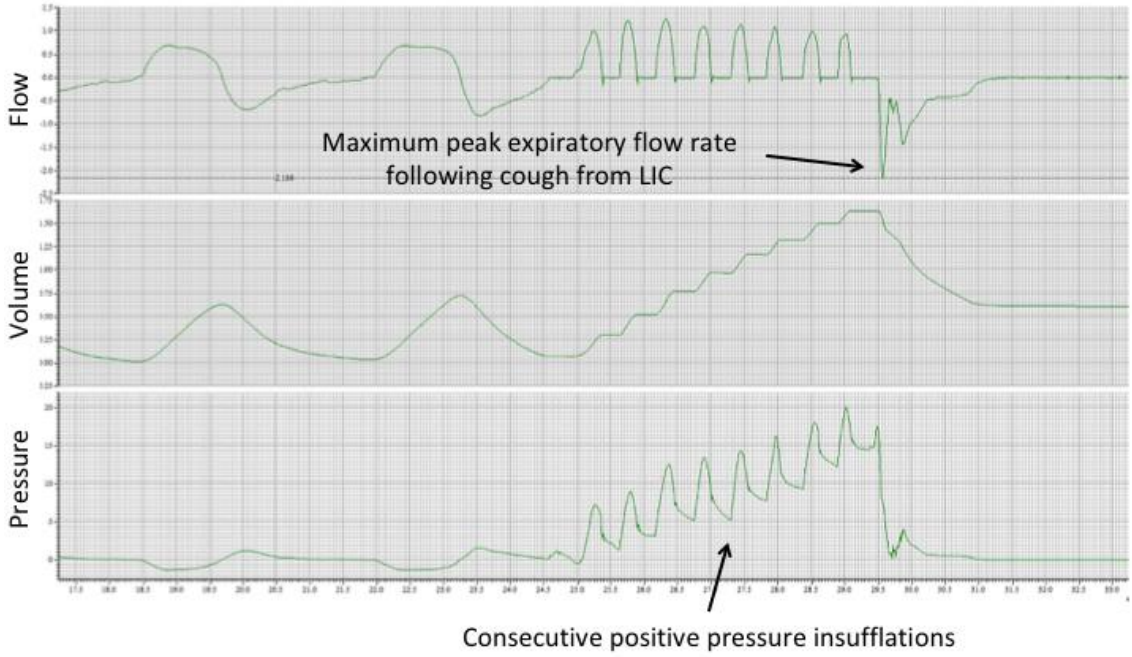

Figure 4-13: Measurement of PCF_{LIC}

Peak cough flow from lung insufflation capacity (PCF_{LIC}) was taken as the maximum peak expiratory flow (in litres per second, later converted to litres per minute) following maximal inflation to LIC using a LVR kit.

4.5 LVR COUNTER DESIGN AND OPERATION

This project's primary aim was to evaluate the effect of LVR on respiratory function over a three-month period. As discussed in Chapter 2, previous research investigating long-term maximal inflation therapy such as LVR has typically relied on self-report. Subjective measures of concordance with therapy may over-estimate actual use.[236,237] An objective measure of LVR use was desired for this project, and was especially important for the exploratory analyses of any potential dose-response effect of LVR.

4.5.1 LVR COUNTER DESIGN SPECIFICATIONS

The custom-built LVR counter, developed by Dr. Doug McKim and Mr. Joao Tomas (The Ottawa Hospital Rehabilitation Centre, Ontario, Canada), comprised a battery-powered digital data logger (Omega® OM-CP-State101A, OMEGA Engineering, Inc.; Stamford, CT, USA), two pressure switches (Model 7411-711, PSF102 Series pressure switch, DesignFlex™ Switches, A World Magnetics Company; Traverse City, MI, USA) and a mount (Figure 4-14).

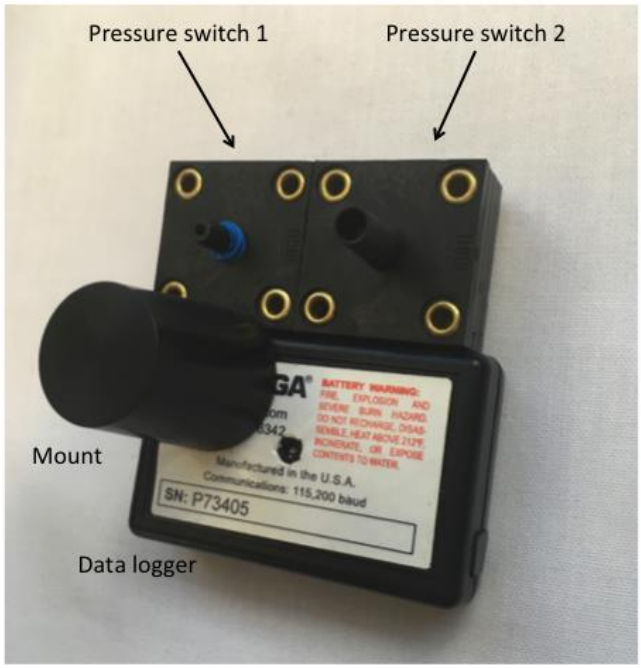

Figure 4-14: Custom-built LVR counter

The data logger recorded state change (i.e., on/off, open/closed), had selectable sampling rates (from 4 Hz to once every 24 hours), a memory capacity of 406,323 readings, multiple start/stop functions and a 10-year battery life. The device accepted input from the pressure transducers via two 2-wire configuration terminal connections, and registered a time-stamped state change, captured as a “0” or “1”, when a voltage change above 2.7 volts or below 0.4 volts was received. The sensitivity of the pressure switches could be adjusted (available range = 1.27 – 5.08 cmH_2O, tolerance ± 0.5 cmH_2O), but were delivered for use pre-set. As constructed, the minimum pressure threshold required to activate the LVR counter under conditions of zero leak was 1.9 ± 0.4 cmH_2O.

The LVR counter was mounted securely to a recess in the LVR kit using 3M™ double-sided adhesive. The pressure switches were connected to the manual resuscitation bag directly via an available proximal port (Switch 1 to Port 1) and distally via a port on the one-way valve using 3-millimetre diameter silicone tubing (Switch 2 to Port 2) (Figure 4-15).

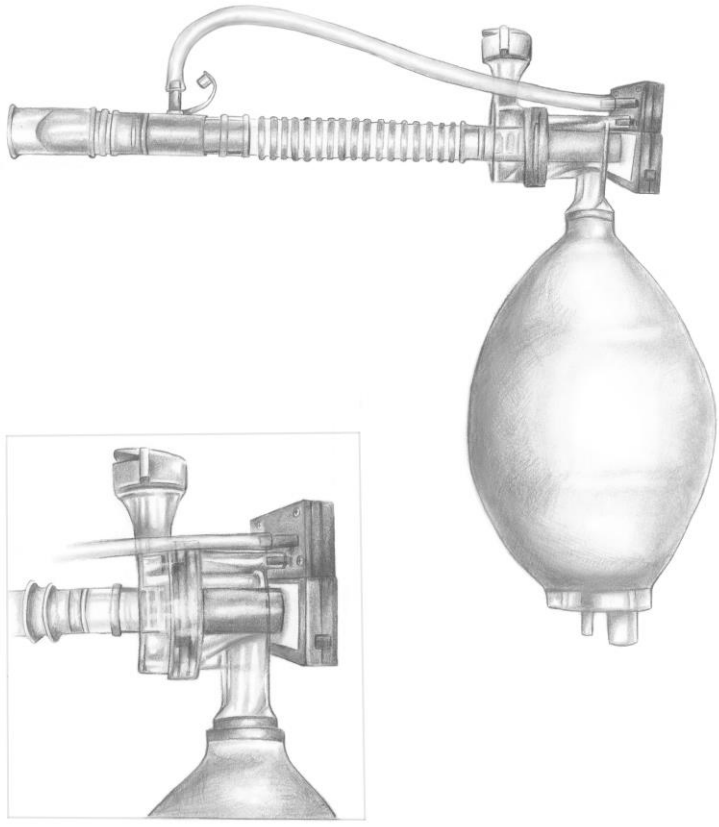

Figure 4-15: LVR counter (insert) attached to LVR kit

The LVR kit was comprised of a self-inflating manual resuscitation bag, tubing, one-way valve, and mouthpiece (item number 1034502; Mercury Medical®; Florida, USA). The LVR counter's first pressure switch connected directly to the LVR bag via an existing port (insert). Additional 3mm silicone tubing connected the second pressure switch to the LVR kit near the mouthpiece (via an existing port on the one-way valve).

When compression of the manual resuscitation bag increased pressure at Port 1 above the pre-set threshold of Switch 1, the pressure switch closed resulting in a voltage change. Similarly, an increase in pressure at Port 2 above the threshold created a voltage change at Switch 2. The device was configured such that Switch 1 and Switch 2 needed to be closed simultaneously to register a state change. If the manual resuscitation bag was compressed (pressure reached at Switch 1) but the mouthpiece remained open to the environment (pressure not reached at Switch 2), this signal was

not recorded by the data logger. Only compression of the bag *and* a closed distal circuit (i.e., mouthpiece sealed) triggered both pressure switches, resulting in the necessary voltage change (state = "0"). When the pressure at Switch 1 or Switch 2 dropped (e.g., compression ceased or mouth opened), the switches would open, registering a state change ("1").

4.5.2 LVR COUNTER SET-UP

The LVR counter was set up at RCT randomisation during the first study visit (Timepoint 0) by the unblinded assessor. The Omega® OM-CP-State101A data logger component was connected via a cable (OM-CP-IFC200 USB and stereo jack connector) to a computer running the proprietary Omega® software (OM-CP Data Logger Software, version 4.2.7.0). Three parameters: i) start/stop mode, ii) sampling rate, and iii) the participant's unique de-identified code were programmed.

The multiple start/stop function was used for this project. In this mode, the LVR counter was in standby but did not commence sampling until manually started by depressing a button on the side of the data logger. Similarly, sampling ceased with a manual stop. This mode was chosen over immediate start or delayed start modes as these would have resulted in continuous recording, exhausting the LVR counter's memory capacity and logging time prior to each monthly follow-up, resulting in unrecorded LVR usage.

In order to determine the optimal sampling rate for this RCT, a bench-test was conducted prior to study recruitment (Section 4.5.3). A value of 1-second was deemed appropriate to measure concordance with LVR therapy during the RCT.

4.5.3 EXPERIMENT: DETERMINING THE OPTIMAL OMEGA® DATA LOGGER SAMPLING RATE

4.5.3.1 BACKGROUND AND AIM

The selectable sampling rates available on the Omega® OM-CP-State101A data logger range from 4 Hz to 24-hourly intervals. The fastest sampling rate of 4Hz provides the most finely grained data, however more frequent sampling also consumes memory capacity, shortening the logging time (Table 4-3).

Sampling rate	Log time (days)	Log time (hours)
4 Hz	2 days, 9 hours, 20 minutes, 38 seconds	57 hours
2 Hz	4 days, 18 hours, 41 minutes, 16 seconds	114 hours
1 Hz	9 days, 13 hours, 22 minutes, 33 seconds	229 hours

Table 4-3: Sampling rate and corresponding log duration of the Omega® data logger

The aim of this bench-test was to determine the optimal sampling rate for capturing LVR use, balancing the need for recording data without exceeding the anticipated memory capacity.

4.5.3.2 METHOD

A standardised session of maximal inflations using a LVR kit fitted with a LVR counter (Section 4.5.1 for design specifications) was conducted under three different sampling rate test conditions:

1. 4 Hz
2. 2 Hz
3. 1 Hz

At each sampling frequency, three sets of LVR with three repetitions but variable compression numbers were performed; two, three and four compressions per

repetition (notated as 2 : 3 : 4 compressions per maximal inflation repetition within a set). The speed of compression also increased across the sets.

The three sampling rate sessions were performed in random order on a healthy volunteer on a single day, with rest periods between each session. An unblinded research assistant programmed the randomly determined sampling rate order into the LVR counter. The clinician performing LVR was thus blinded to the test condition.

The number of compressions and repetitions recorded by the LVR counter were compared to the actual delivered (3 sets of 3 repetitions = 9 repetitions per test condition; comprising total of 27 compressions).

4.5.3.3 RESULTS

A sample of a downloaded data file (sampling rate set at 4Hz) is shown in Figure 4-16. For all sampling rates, the recorded state changes accurately identified that three sets of three maximal inflation repetitions had been delivered. Individual resuscitation bag compressions delivered at a slow or moderate pace were accurately captured at sampling rates of 4Hz or 2Hz. Only the fastest sampling frequency of 4Hz recorded every bag compression when they were performed quickly (Table 4-4).

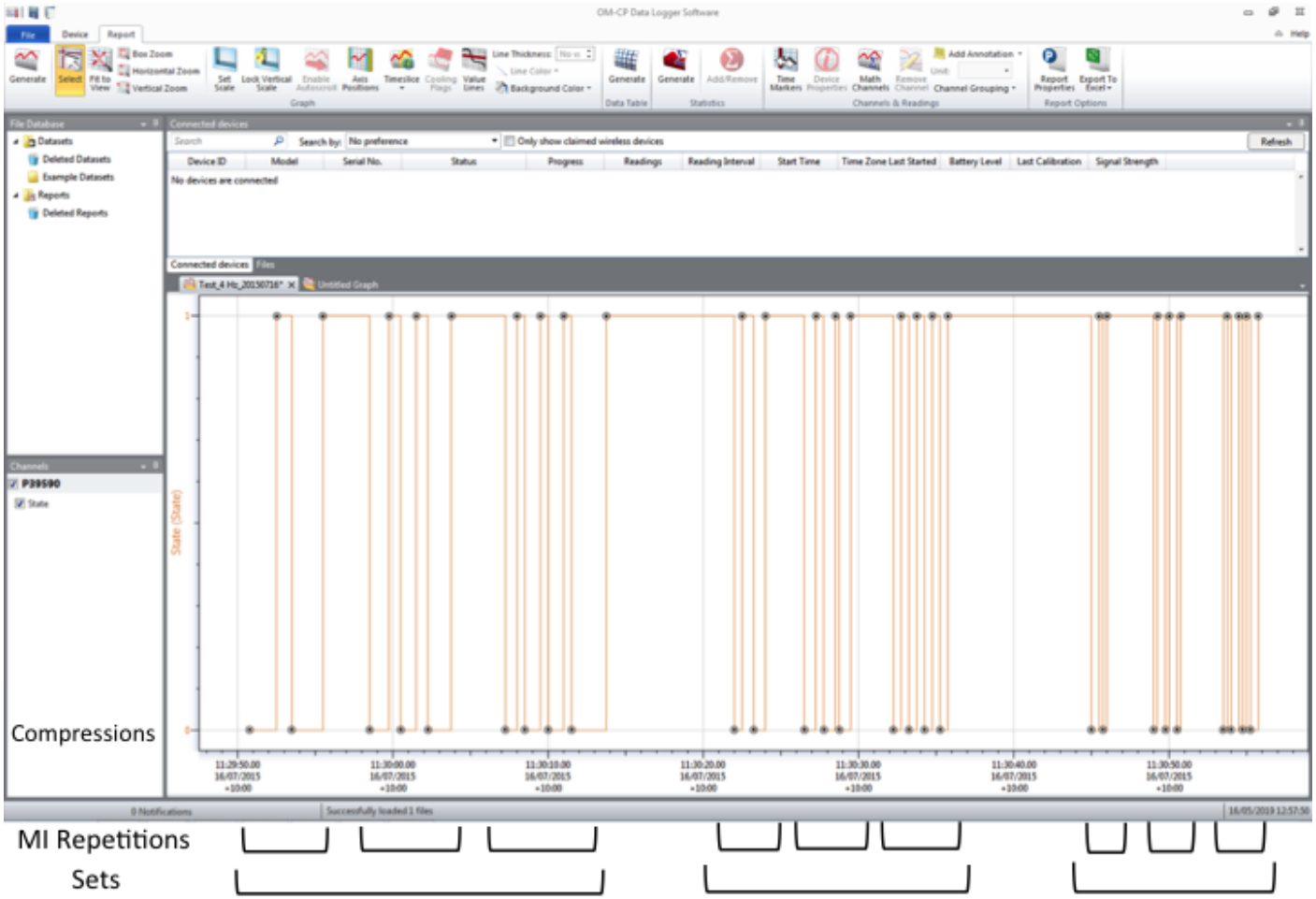

Figure 4-16: Omega® data file, at 4 Hz sampling rate
Small dots demonstrate the state change associated with resuscitation bag compression. Three sets of three maximal inflations (MI repetitions) can be identified, with 2, 3 and then 4 compressions per repetition. Note increase in speed of compressions over the test protocol.

Delivered pattern 3 reps per set	Sampling rate = 4Hz	Sampling rate = 2Hz	Sampling rate = 1 Hz
Set 1 (slowest) *2 : 3 : 4*	2 : 3 : 4	2 : 3 : 4	2 : 2 : 4
Set 2 *2 : 3 : 4*	2 : 3 : 4	2 : 3 : 4	1 : 2 : 2
Set 3 (fastest) *2 : 3 : 4*	2 : 3: 4	2 : 2 : 3	1 : 1 : 1
Total state changes n(%) (expected = 27)	27 (100%)	25 (93%)	16 (59%)
Session duration	66 seconds	69 seconds	64 seconds
Interpretation of dosage	3 reps x 3 sets	3 reps x 3 sets	3 reps x 3 sets

Table 4-4: State changes recorded by the LVR counter at tested sampling rates

Where x : y : z = indicates the number of compressions per maximal inflation within each set. Shaded cells indicate discordance between captured compressions and delivered compressions.

4.5.3.4 DISCUSSION

Programming the LVR counter at the highest resolution (4 Hz) accurately recorded all aspects of the LVR therapy: the number of compressions per maximal inflation, the number of maximal inflations (repetitions) in a set, and the total number of sets performed. At sampling rates of 1 and 2 Hz, concordance between the number of maximal inflations per set and the number of sets recorded was also demonstrated. However, the ability to detect the number of compressions was reduced, especially at 1 Hz and when the manoeuvres were performed faster.

Given the aim of the LVR counter is to provide an objective measure of LVR use during the three-month RCT, and all three tested sampling frequencies recorded the date, time and duration of LVR use, a sampling rate of 1 Hz was chosen. One second reflects an appropriate balance between obtaining detailed data and providing a conservative buffer in the device's memory capacity. Selecting a higher sampling rate will record the number of compressions per therapy session with greater precision, however if participants perform the intervention more frequently, forget to manually stop the

LVR counter between sessions, skip a monthly assessment or not have their device downloaded and re-programmed monthly, logging time may be higher than estimated. Subsequent sessions would not be recorded and therapy use underestimated. A 1Hz sampling frequency enabled recording of LVR use (Y/N), session duration, number of sessions per day, cumulative therapy time per day, total number of sessions and total days used during the study.

4.5.4 LVR COUNTER OUTPUT

The LVR counter was downloaded at Timepoints 1, 2 and 3b by the unblinded assessor, by connecting the Omega® OM-CP-State101A data logger component to a computer running the proprietary Omega® software via a cable. Data was de-identified at source, saved as a proprietary data file (.mtff) and later converted to Excel format (.xlsx). After study completion, a custom-written Excel macro was used to convert the raw data output (date (dd/mm/yyyy format), time (hh:mm:ss) and Channel 1 state (1 or 0) where "0" represented a compression of the manual resuscitation bag) to summary data. Session-level summary data was expressed as date, session start time, session end time, session length (hh:mm:ss) and number of compressions counted within a session. Participant-level summary data was expressed as number and duration of LVR sessions per day (Excel macro detailed in Appendix 11.1.4).

5 METHODS: DEVELOPMENT & VALIDATION OF C_{RS} MEASUREMENT

5.1 BACKGROUND

Measuring C_{rs} in an ambulatory setting has not previously been reported, however for this research study we required a non-invasive measure that could be conducted using portable equipment in a non-laboratory environment. This chapter details the pulse inflation method of measuring C_{rs}, and the derivation and validation of the rules developed to analyse pulse inflation manoeuvres. The methods were developed from the published work of Suratt and colleagues,[77] along with personal communication with Mr. Yannick Molgat-Seon.[78]

5.2 C_{RS} MEASUREMENT PROCEDURE

Participants were tested in the seated position, using the circuit described in Section 4.3, Figure 4-7. An oro-nasal mask interface was selected rather than a mouthpiece and nose clip due to anticipated bulbar muscle involvement in some of the trial participants. The potential effect of interface on C_{rs} measurements was tested on a non-NMD affected volunteer and found to not substantially affect the values obtained. Mean ± SD values for C_{rs} using a mouthpiece and nose clip were 0.0557 ± 0.0102 L/cmH_2O compared to 0.0500 ± 0.0081 L/cmH_2O (Student's paired *t*-test $p = 0.18$).

The testing procedure was explained to participants prior to commencement. The measurement circuit was placed on the participant with the spontaneous limb open (Section 4.3); the assessor controlled the tap whilst an assistant sealed the oro-nasal mask to the participant's face. Participants were instructed to breathe gently (i.e., spontaneous tidal volume breaths) for three to five breaths, and then relax. After exhaling to approximate FRC, the assessor manually operated the tap to deliver a constant inflation airflow at a known flow rate. Participants were coached to cease any active respiratory efforts and allow the pulse of air to passively inflate their lungs. Flow

was commenced at 0.3 L/s and modified if necessary[79] to match the participant's flow rate, minimise visible respiratory efforts, and produce a linear pressure-time signal. The duration of the pulse inflation was controlled by the assessor; inflation continued until a volume greater than tidal breathing but less than a maximal inflation was delivered, confirmed by examining the real-time pressure and volume signals. Prolonged pulse durations were avoided as these could potentially recruit areas of atelectatic lung and alter compliance. Cessation of inflation and passive exhalation occurred by returning the tap to the starting position (Figure 5-1).

A minimum of ten inflation manoeuvres were obtained during each C_{rs} test.

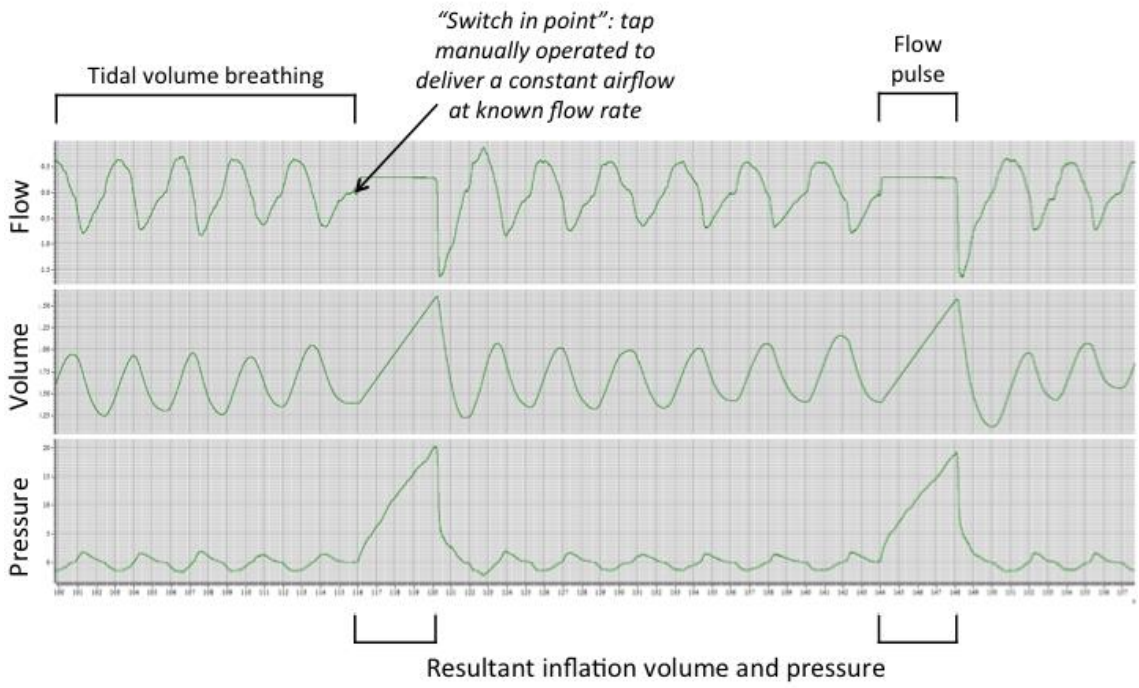

Figure 5-1: Measurement of C_{rs}

Respiratory system compliance (C_{rs}) was measured using the pulse inflation method. Each test generated flow (L/sec), volume (L) and mouth pressure (cmH_2O) traces as illustrated above. Traces were scored as per the Scoring rules (Section 5.5) to determine C_{rs}; a pressure-volume curve was generated (X-Y plot) for each inflation manoeuvre, with the line of best fit (least squares regression) representing the slope and hence C_{rs} value.

5.3 SIGNAL ANALYSIS: C_{RS}

Individual inflation manoeuvres were scored by one of three members of the research team who were blinded to randomisation group (RD, AR, NS), according to the scoring rules below (Section 5.5). All scorers underwent additional training and assessment of intra- and inter-rater reliability prior to graduating to independent scoring (Appendix 11.2).

All scoring occurred on de-identified participant data. The order in which tests were scored was randomised across all participants and timepoints using a randomisation schedule to minimise the effects of learning or fatigue on manual scoring.

All technically acceptable pulse inflation manoeuvres within a timepoint were used to calculate summary C_{rs} values. The mean, SD, coefficient of variation (CV) and number of acceptable trials were recorded. If the CV of the manoeuvres was greater than 40%, all manoeuvres within the C_{rs} test session were reviewed by a second, more experienced assessor (NS). This value was selected based on findings from the derivation and validation samples (Section 5.4 and Section 5.6); the largest CV of the manoeuvres within a single C_{rs} testing session, when all acceptable trials were included in the summary C_{rs} score, was noted to be 40%. At this level of within-participant variance, there remained strong intra- and inter-rater agreement of the C_{rs} summary value. Therefore, any summary value that was associated with a CV larger than 40% was reviewed by a second person to minimise scoring error.

Prior to data analysis for each study component (Chapter 6, Chapter 7, Chapter 8), the mean C_{rs} values underwent a second round of quality control.[286] Serial measurements were compiled, the difference between pairs of consecutive timepoints calculated and expressed as percentage change (e.g., mean C_{rs} value at Timepoint 1 minus Timepoint 0a, divided by Timepoint 0a). If the percentage change across timepoints was greater than 40%, a second assessor (NS) reviewed the C_{rs} test sessions in question to confirm this magnitude of change over time.

5.4 EXPERIMENT: DERIVATION OF THE C_{RS} SCORING RULES

5.4.1 METHOD: DERIVATION SAMPLE

Respiratory system compliance tests from seven participants: six participants with NMD and one non-NMD affected volunteer, were selected from the larger group of study participants to represent a range of NMD and quality of traces. Each person's C_{rs} test comprised ten C_{rs} manoeuvres, providing 70 individual C_{rs} manoeuvres to score. This "derivation sample" was independently analysed by four scorers experienced in reviewing C_{rs} manoeuvres (NS, PR, PN, SH) on three different days (scoring sessions). Test order was fixed and scorers were blinded to clinical data. Signal display (Spike2 (version 7)) was standardised to show the calibrated flow, pressure and volume signals, and for each manoeuvre a X-Y plot was created to generate a pressure-volume (P-V) curve and line of best fit (least squares regression).

Scorers were provided with the same general instructions, but no specific advice regarding principles of scoring or steps involved. Scorers constructed the P-V curve from a segment of each pulse inflation, which they selected. The flow rate, gradient of the regression line (C_{rs} value), the regression R^2, durations of the pulse inflation and selected linear segment were recorded. The mean C_{rs} value of all acceptable manoeuvres as determined by the scorer (minimum of three) was calculated and used as the summary value for statistical analyses. The SD and CV were also calculated. If only one or two trials were deemed acceptable from the C_{rs} test, no summary values were recorded and the test result displayed as "N/A" (not available).

5.4.2 ANALYSIS: DERIVATION SAMPLE

To assess conformity between the four scorers, the C_{rs} summary value calculated for each participant on a given scoring session was compared using an intraclass correlation coefficient (ICC). For the derivation sample, inter-rater reliability was analysed using a two-way mixed-effects model of absolute agreement for the mean of ratings, as we wished to evaluate the level of consensus between the four specific scorers. Intra-rater reliability was similarly evaluated using a two-way mixed effects model ICC.

The steps each scorer took to score and determine acceptability, along with the results of the reliability analysis, were discussed in a wider forum to establish the scoring rules. Forum members were selected from experienced respiratory physicians, scientists and physiotherapists of the Department of Respiratory and Sleep Medicine, Austin Health.

5.4.3 RESULTS: DERIVATION SAMPLE

Each scorer scored the derivation sample of seven individual C_{rs} tests, comprising ten C_{rs} manoeuvres each, during three separate scoring sessions. An example of the summarised data from one scorer for one scoring session is illustrated in Table 5-1. Group results are presented in Table 5-2.

Participant	Pulse flow (L/s)	Included manoeuvres (n)	Mean C_{rs} (L/cmH_2O)	SD C_{rs} (L/cmH_2O)	CV C_{rs} (%)	R^2 of line	Mean duration of sampled section (sec)
1	0.28	4	0.0044	0.0002	5.94	>0.99	0.35
2	0.32	5	0.0246	0.0036	14.53	>0.99	0.47
3	0.31	10	0.0659	0.0094	14.25	>0.99	2.54
4	0.33	10	0.0093	0.0007	7.18	>0.99	0.58
5	0.36	8	0.0401	0.0087	21.62	0.99	0.72
6	0.38	4	0.0210	0.0006	2.88	>0.99	0.57
7	0.29	7	0.0177	0.0017	9.75	0.99	0.60

Table 5-1: Representative summarised data of the Derivation sample

From Scorer A for a single scoring session

C_{rs} = total respiratory system compliance, SD = standard deviation, CV = coefficient of variation. Each participant test comprised ten C_{rs} manouevres. (n) = number of acceptable manoeuvres constituting the mean C_{rs} score.

Scorer	Participant	Session 1 C_{rs} summary value	Session 2 C_{rs} summary value	Session 3 C_{rs} summary value	Intra-rater ICC
A	1	0.0051	0.0037	0.0044	0.99
	2	0.0277	0.0259	0.0246	(0.98, >0.99)
	3	0.0614	0.0632	0.0659	***p*<0.0001**
	4	0.0096	0.0096	0.0093	
	5	0.0406	0.0503	0.0401	
	6	0.0209	0.0202	0.0210	
	7	0.0191	0.0170	0.0177	
B	1	0.0063	0.0078	0.0042	>0.99
	2	0.0272	0.0272	0.0268	(0.99, >0.99)
	3	0.0618	0.0604	0.0586	***p*<0.0001**
	4	0.0104	0.0092	0.0091	
	5	0.0379	0.0453	0.0399	
	6	0.0186	0.0190	0.0176	
	7	0.0181	0.0182	0.0171	
C	1	0.0037	0.0059	0.0061	>0.99
	2	0.0338	0.0316	0.0269	(0.98, >0.99)
	3	0.0635	0.0619	0.0638	***p*<0.0001**
	4	0.0094	0.0094	0.0093	
	5	0.0538	0.0453	0.0467	
	6	0.0201	0.0198	0.0202	
	7	0.0167	0.0177	0.0196	
D	1	0.0037	0.0032	0.0030	0.99
	2	0.0280	0.0328	0.0274	(0.96, >0.99)
	3	0.0647	0.0668	0.0641	***p*<0.0001**
	4	0.0093	0.0094	0.0096	
	5	0.0521	0.0504	0.0694	
	6	0.0198	0.0196	0.0192	
	7	0.0198	0.0185	0.0233	
Inter-rater ICC		0.99 (0.98, >0.99) ***p*<0.0001**	0.99 (0.99, >0.99) ***p*<0.0001**	0.98 (0.95, >0.99) ***p*<0.0001**	

Table 5-2: Inter- and intra-rater reliability of scorers scoring the derivation sample

Total respiratory system compliance (C_{rs}) summary value (L/cmH_2O) calculated for each participant, on each scoring session, by each scorer. The summary value represents the mean of all acceptable traces in that test session. Inter-rater and intra-rater intraclass correlation coefficient (ICC) estimates (95% confidence interval) based on mean ratings, two-way mixed-effects model with absolute agreement. *P*-values <0.05 were statistically significant **(bold)**.

5.5 C_{RS} SCORING RULES

Following the forum discussion and review of reliability, the following rules for scoring C_{rs} from pulse inflation manoeuvres were determined:

1. Assess quality of manoeuvre
    a. Consistency of flow during pulse inflation

       Disregard manoeuvre if flow rate is not constant
2. Assess linearity of the pressure-time signal during pulse inflation
    a. Good = linear throughout entire pulse inflation
    b. Fair = linear segments with different gradients
    c. Poor = multiple segments with no clear linear portion

       Disregard manoeuvre if linearity is poor
3. Construct pressure-volume (P-V) curve of the "most linear" portion of the pulse inflation using the pressure-time signal. If there are two clear linear segments with different gradients, take the latter segment[79]
4. Record Slope and R-squared value of the regression line (line of best fit) of the P-V curve
5. Record duration of the sampled segment and of the delivered pulse inflation
6. Report the C_{rs} summary value by calculating the mean of all acceptable pulse inflation manoeuvres (constant flow plus good or fair quality signal), from a minimum of three satisfactory manoeuvres. Also report the SD and CV.

The decision to select a segment of the pulse inflation from which to derive C_{rs}, as opposed to only calculating C_{rs} from manoeuvres that were linear throughout the entire pulse inflation[78] was supported by findings of Suratt and colleagues. In their sample of nine ventilated patients, they disregarded the first portion of any pulse inflation curves that were non-linear (suggesting respiratory muscle activity) and calculated C_{rs} using the latter linear segment. There was strong correlation between static, invasively-derived C_{rs} and pulse C_{rs} values (r=0.997) regardless of duration but providing the selected portion was linear. This suggests that C_{rs} can be accurately calculated from part of a manoeuvre.[79]

5.6 EXPERIMENT: VALIDATION OF THE CRS SCORING RULES

5.6.1 METHOD: VALIDATION SAMPLE

To validate the newly developed scoring rules, a "validation sample" of C_{rs} test results from three randomly selected participants was compiled. Three scorers (NS, SH, RD) scored the validation sample on three different days (scoring sessions), using the scoring rules above (Section 5.5). The order the tests were presented in was randomised on each day and scorers were blinded to participant and clinical data. Intra-rater reliability was performed as per the derivation sample, however inter-rater reliability employed a two-way random-effects model ICC, as we wished to determine consensus between any trained scorers.

5.6.2 RESULTS: VALIDATION SAMPLE

Each scorer scored the validation sample of three individual C_{rs} tests, comprising ten C_{rs} manoeuvres each, during three separate scoring sessions, according to the scoring rules developed. An example of the summarised data from one scorer for one scoring session is illustrated in Table 5-3. Summary data are presented in Table 5-4.

Participant	Pulse flow (L/s)	Included manoeuvres (n)	Mean C_{rs} (L/cmH_2O)	SD C_{rs}	CV C_{rs}	R^2	Mean duration of sampled section (sec)
1	0.44	5	0.0508	0.0073	14.47	>0.99	0.48
2	0.38	10	0.0195	0.0031	15.84	>0.99	0.38
3	0.28	10	0.0095	0.0009	10.00	>0.99	0.61

Table 5-3: Representative summarised data of the Validation sample

From Scorer A for a single scoring session

C_{rs} = total respiratory system compliance, SD = standard deviation, CV = coefficient of variation. Each participant test comprised ten C_{rs} manouevres. (n) = number of acceptable manoeuvres constituting the mean C_{rs} score.

Scorer	Participant	Session 1 C_{rs} summary value	Session 2 C_{rs} summary value	Session 3 C_{rs} summary value	Intra-rater ICC
A	1	0.0499	0.0506	0.0508	>0.99
	2	0.0192	0.0191	0.0195	(>0.99, >0.99)
	3	0.0096	0.0096	0.0095	***p*<0.0001**
B	1	0.0413	0.0392	0.0510	0.99
	2	0.0184	0.0182	0.0192	(0.87, >0.99)
	3	0.0097	0.0092	0.0094	***p*<0.0001**
C	1	0.0370	0.0410	0.0373	>0.99
	2	0.0180	0.0192	0.0200	(0.97, >0.99)
	3	0.0095	0.0090	0.0090	***p*<0.0001**
Inter-rater ICC		0.98 (0.88, >0.99) ***p*<0.001**	0.99 (0.90, >0.99) ***p*<0.001**	0.98 (0.86, >0.99) ***p*<0.001**	

Table 5-4: Inter- and intra-rater reliability of scorers scoring the validation sample

Total respiratory system compliance (C_{rs}) summary value (L/cmH_2O) calculated for each participant, on each scoring session, by each scorer. The summary value represents the mean of all acceptable traces in that test session. Order of participants was randomised within each scoring session. Inter-rater intraclass correlation coefficient (ICC) estimates (95% confidence interval) based on mean ratings, two-way random-effects model with absolute agreement. Intra-rater intraclass correlation coefficient (ICC) estimates (95% confidence interval) based on mean ratings, two-way mixed-effects model. *P*-value <0.05 considered statistically significant (in **bold**).

5.7 DISCUSSION: DEVELOPMENT OF A MEASURE OF TOTAL RESPIRATORY SYSTEM COMPLIANCE

Assessing C_{rs} is key to the knowledge this thesis aims to produce regarding respiratory function in people with NMD and the effect of LVR therapy. Existing methods for measuring C_{rs} are invasive and/or have only been conducted in a respiratory laboratory. A fundamental ethos of this research project, enabling participation, required that this involved, physiological outcome measure be conducted in a participant's home. Therefore, the pulse inflation method was developed as detailed above.

One of the minor changes made to the original, published pulse inflation technique, which used a flow of 0.30 L/s,[77] was adjustment of the pulse inflation rate. This was necessary to match each participant's demand to the ensuing flow, as flow rates less than inspiratory demand resulted in respiratory efforts in some participants and a non-linear response to the inflation. This was also noted by Molgat-Seon and colleagues (personal communication of unpublished work, 18/01/2019) and the original work by Suratt and colleagues.[77,79] Flow rates in the derivation and validation samples used for developing the scoring rules ranged between 0.28 and 0.44 L/s (mean ± SD = 0.34 ± 0.05 L/s), similar to that used by previous authors. This attention to matching inspiratory flow demand resulted in three or more acceptable manoeuvres and hence summary values for most trials over the course of this research project.

Strong agreement in analysing the derivation sample was observed between all four scorers, suggesting that they followed similar principles in calculating C_{rs} from each manoeuvre. Inter- and intra-rater reliability for each of the three scoring sessions were excellent in both the derivation (Section 5.4) and the validation sample (Section 5.6), suggesting that the rules effectively standardised the manual scoring process required for C_{rs} measurement. These samples also constituted a library of manoeuvres that were used for training (the derivation sample) and assessment of scorers (the validation sample), prior to undertaking any analysis of de-identified participant study data.

In summary, by further developing the non-invasive pulse method, we procured a measure of C_{rs} that could be conducted in participants with NMD in a non-laboratory setting. Standardised scoring rules were developed, validated and used to score the 456 C_{rs} testing sessions and approximately 4560 individual pulse inflations conducted during the course of this research project.

6 RESPIRATORY FUNCTION IN PEOPLE WITH NMD: BASELINE CHARACTERISTICS

6.1 INTRODUCTION

As discussed in Chapter 2, respiratory complications are a common cause of morbidity and mortality in many NMDs. Muscle weakness and concomitant impairment of the respiratory system impact on the persons' ability to take a very deep breath and cough effectively. Hypercapnia, respiratory failure, the need for home mechanical ventilation and mortality rise as lung volume falls.[4,179,181,184]

Characterising respiratory dysfunction and better understanding the contributing mechanisms may help target interventions to improve respiratory symptoms and clinical outcomes. Findings from small studies in participants with NMD suggest that the degree of lung volume restriction is disproportionately greater than that expected due to respiratory muscle weakness alone.[143,147,152] Stiffening of the lung and chest wall have been implicated,[149,152] however there are few studies that have measured C_L, C_{CW} or C_{rs} in slowly-progressive NMD and none have included C_{rs} in people with MND. Investigating the relationships between lung volumes, C_{rs}, respiratory muscle strength and cough in a larger clinical cohort may provide further insights. Comparing respiratory function characteristics between a rapidly-progressive condition and people who have lived with a NMD for many years may identify important differences that could substantially contribute to our knowledge of respiratory physiology in this collection of diseases.

Furthermore, although it is accepted that respiratory morbidity is associated with NMDs if respiratory involvement is present, the incidence of RTIs is not well established. Between 9% to 75% of research trial participants with MND had a RTI within observation periods of 12 to 50 months.[105,111,190,191] Other cross-sectional studies looking at the retrospective incidence in other, more slowly-progressive forms of NMD have placed the average rate of RTI between 0.62 to 0.84

episodes/patient/year,[167,168] whereas a large longitudinal cohort study conducted throughout the province of Ontario, Canada found that 22% of adults with NMD visited the emergency department on average 1.6 times every three years for respiratory complications.[28] The large variability between these published reports indicates that the frequency of this respiratory complication remains undetermined.

A "poor cough" has been associated with past history of RTIs, however the evidence underpinning this assertion is not strong. Studies have relied on self-report of episodes, sometimes dating back decades, and then concluded that the current PCF is associated with past history of pneumonia[168] or hospitalisation for acute respiratory distress.[194] Peak cough flow values have been interpreted as having clinical significance; for example a PCF <160 L/min is a sign of an ineffective cough, and a value <270 L/min places one at risk of developing a RTI. Thresholds have been incorporated into consensus statements to guide the initiation of cough augmentation strategies.[10-12,53,54,187] However as detailed earlier in this thesis, the source data have limitations and these thresholds are based largely on expert consensus. This is not to say that respiratory function and markers of this are *not* related to respiratory complications, only that more work is necessary to add to this understanding of any relationships. Adding to this evidence-base and understanding of RTIs in people living with NMD is important; respiratory function assessment may predict one's risk of developing a RTI, informing clinical decision-making and timing of interventions such as NIV and cough augmentation techniques.

Thus, there are three aims for this chapter. The first is to describe respiratory function in a cohort of people with MND and other NMDs. The second is to investigate the relationships between lung volumes, C_{rs}, respiratory muscle strength and PCF, particularly with regards to disease type. The third aim is to report on past history of RTI within this cohort and associations between RTI and respiratory function, including the discriminatory ability of PCF and VC to identify people who reported an event.

6.2 NULL HYPOTHESES

1. That respiratory function will not be different between people living with MND and people living with other NMDs.
2. That there are no relationships between cough, lung volume, respiratory muscle strength or total respiratory system compliance.
3. That a) the presence of a respiratory tract infection in the past year is not related to underlying respiratory function, and b) VC or PCF values at routine assessment can not identify people who reported an episode in the past.

6.3 METHODS

This observational cross-sectional study comprised baseline data from the research project outlined in Chapter 3. Demographic, respiratory information and respiratory function tests were collected during the initial assessment (Timepoint 0a) as per Section 3.6 and Table 6-1. Equipment, procedures and measurement methods were detailed in Chapters 4 and 5.

	Timepoint 0a	Timepoint 0b	Timepoint 1	Timepoint 2	Timepoint 3a	Timepoint 3b
Time	Time 0, Ax (a)	Time 0, Ax (b)	1-month	2-month	3-month, Ax (a)	3-month, Ax (b)
Location	Austin Health		Participant's Home	Participant's Home	Austin Health	
Duration	5-6 hours		2-3 hours	2-3 hours	5-6 hours	
Measures						
Demographic information	✓				✓	
Respiratory information	✓				✓	
VC	✓	✓	✓	✓	✓	✓
PCF	✓	✓	✓	✓	✓	✓
FVC, FEV_1	✓				✓	
MIP, MEP, SNIP	✓				✓	
Static lung volumes	✓	✓	✓	✓	✓	✓
C_{rs}	✓	✓	✓	✓	✓	✓
LIC	✓	✓	✓	✓	✓	✓
PCF_{LIC}	✓	✓	✓	✓	✓	✓
SRI	✓				✓	
AQoL-8D	✓				✓	
ALSFRS-R	✓ if MND				✓ if MND	
Other		Randomised Training session	Treatment review	Treatment review		Treatment review Usual care session

Table 6-1: Schedule of data collection: Observational cross-sectional study

Shaded cells represent components applicable to this sub-study. Ax (a) = pre-session assessment, Ax (b) = post-session assessment. VC = vital capacity, PCF = peak cough flow, FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 second, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure, SNIP = sniff nasal inspiratory pressure, C_{rs} = respiratory system compliance, LIC = lung insufflation capacity, PCF_{LIC} = peak cough flow from lung insufflation capacity. SRI = Severe Respiratory Insufficiency questionnaire, AQoL-8D = Assessment of Quality of Life questionnaire, ALSFRS-R = Revised Amyotrophic Lateral Sclerosis Functional Rating Scale, MND = motor neurone disease.

6.4 RESULTS

6.4.1 PARTICIPANTS

Eighty consecutive participants were recruited (Figure 6-1), with MND constituting the largest single disease (34%) (Table 6-2). Although five recruited participants met the study inclusion criterion of FVC <80% of predicted normal, this screening lung capacity value was greater than the lower limit of normal (LLN) using the Global Lung Function Initiative (GLI) data[244] (Table 11-4, Appendix 11.3.1). Home mechanical ventilation and routine respiratory physiotherapy were used by 78% and 12% of participants respectively (Table 6-3).

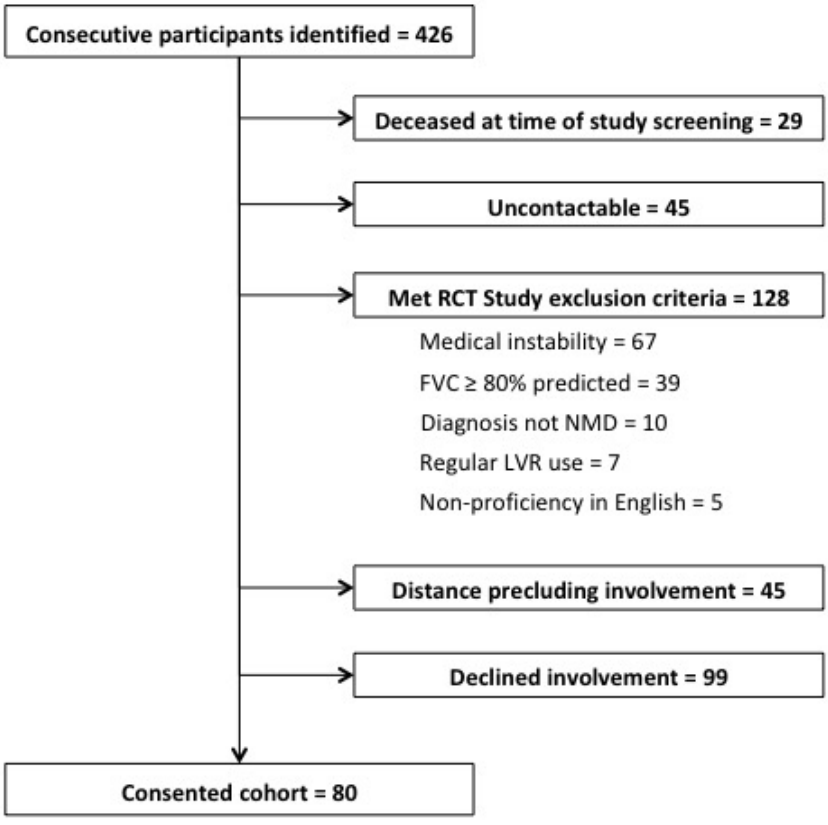

Figure 6-1: Study recruitment flow chart

RCT = randomised controlled trial, FVC = forced vital capacity, NMD = neuromuscular disease, LVR = lung volume recruitment

Variable	All (n=80)	MND (n=27)	Other (n=53)	*p*-value
Age (years)	59.2 (31.8 – 68.0)	65.9 (59.2 – 71.2)	48.7 (27.0 – 65.1)	**0.0002**
Gender (M:F)	44 : 36	19 : 8	25 : 28	**0.049**
Height (cm)	165.9 ± 14.8	173.3 ± 9.1	162.1 ± 15.7	**0.001**
BMI (kg/m^2)	24.8 ± 7.1	25.9 ± 5.4	24.2 ± 7.9	0.301
Age at symptom onset (years)	26.1 (4.5 – 63.3)	63.7 (56.2 – 68.2)	9.6 (3.4 – 24.2)	**<0.0001**
Time since symptom onset (years)	14.4 (2.2 – 25.5)	1.9 (1.2 – 3.0)	22.6 (15.4 – 44.2)	**<0.0001**
NIV user (Y:N)	62 : 18	20 : 7	42 : 11	0.600
Gastrostomy (Y:N:F)	21 : 57 : 2	17 : 8 : 2	4 : 49	**<0.0001**
ALSFRS-R score		24.2 ± 7.6		
ALSFRS-R respiratory sub-score		4.2 ± 3.7		
ALSFRS-R bulbar sub-score		8.9 ± 3.4		
ALSFRS-R bulbar score ≤9 (Y:N)		12 : 15		
ALSFRS-R fine motor sub-score		5.4 ± 3.7		
ALSFRS-R gross motor sub-score		5.7 ± 3.9		

Table 6-2: Demographic data by sub-group

Data are presented as mean ± standard deviation, median (lower quartile – upper quartile) or frequency count. *P*-values represent Student's independent two-sample *t*-test for comparison of means, Mann-Whitney two-sample *U*-statistic for non-normally distributed data or Fisher's exact test for proportions. Data in **bold** indicate statistically significant values ($p<0.05$). MND = motor neurone disease, Other = Other neuromuscular disease. M = male, F = female, BMI = body mass index, NIV = non-invasive ventilation, Y=yes, N=no, F=failed gastrostomy procedures. ALSFRS-R = Revised amyotrophic lateral sclerosis functional rating scale. Bulbar sub-score ≤9 indicates moderate bulbar symptoms as per Smith 2018.[287]

Disease type & diagnoses		
MND	Amyotrophic lateral sclerosis / MND	27
Other	Chest wall disease	11
	Muscular dystrophies	11
	SMA	8
	DMD	5
	Myotonic dystrophy	4
	Diaphragm palsy	4
	PPS	3
	Charcot-Marie-Tooth disease	2
	Primary lateral sclerosis	2
	Multiple sclerosis	2
	Long-standing SCI	1
Ventilation type		
	None	18
	NIV nocturnally	53
	NIV nocte + daytime	8
	CPAP	1
Respiratory physiotherapy		
Routine use	None	62
	Started if signs of impending illness	12
	Daily deep breathing	6
Cough augmentation	Glossopharyngeal breathing	2
	Manually assisted cough	3
	Mechanical insufflation-exsufflation	2
	None	73

Table 6-3: Study cohort

Disease type sub-groups with corresponding diagnoses, use of ventilation and respiratory physiotherapy

Data are presented as frequency count.

MND = motor neurone disease, SMA = spinal muscular atrophy, DMD = Duchenne muscular dystrophy, PPS = post-polio syndrome, SCI = spinal cord injury, NIV = non-invasive ventilation, CPAP = continuous positive airway pressure.

6.4.2 RESPIRATORY FUNCTION

Participants had severely reduced lung volumes and weak respiratory muscles (group mean VC = 41 ± 19% predicted normal value, TLC = 45 ± 17%, MIP = 44 ± 26%, MEP = 42 ± 22%) (Table 6-4). Vital capacity (Figure 6-2) and static lung volumes were lower in people with Other NMD compared to MND. Absolute lung volumes were significantly reduced between disease types, however there was no difference in the *relative* contribution of IC, ERV, RV or FRC to TLC (Table 6-4). Participants with MND had higher C_{rs} than those in the Other NMD sub-group (Figure 6-3), however when C_{rs} was expressed relative to participant lung volume (FRC), no differences in specific C_{rs} were found between disease types (Table 6-4).

Mean PCF for the group as a whole was 177 ± 69 L/min (range = 61 to 492 L/min), and was comparable between-disease types. Similarly, MIP, MEP and SNIP values were similar between participants with MND and Other NMDs (Table 6-4).

Variable	All		MND		Other		*p*-value
VC (L)	1.58 ± 0.85	80	2.12 ± 0.75	27	1.30 ± 0.77	53	**<0.0001**
VC (%pn)	41.1 ± 18.6	80	53.1 ± 15.4	27	35.0 ± 17.2	53	**<0.0001**
PCF (L/min)	177.1 ± 69.0	80	187.4 ± 61.3	27	171.9 ± 72.6	53	0.346
MIP (cmH_2O)	39.1 ± 20.6	77	37.8 ± 19.5	25	39.8 ± 21.3	52	0.693
MIP (%pn)	44.4 ± 25.7	77	39.1 ± 19.2	25	47.0 ± 28.1	52	0.209
MEP (cmH_2O)	49.3 ± 26.5	69	50.8 ± 27.1	21	48.7 ± 26.4	48	0.767
MEP (%pn)	42.4 ± 21.9	69	39.7 ± 18.6	21	43.5 ± 23.3	48	0.505
SNIP (cmH_2O)	26.0 ± 13.7	78	22.5 ± 9.5	26	27.7 ± 15.2	52	0.119
SNIP (%pn)	27.7 ± 14.7	78	24.2 ± 10.1	26	29.4 ± 16.4	52	0.137
C_{rs} (L/cmH_2O)	0.0377 ± 0.0251	72	0.0473 ± 0.0241	23	0.0331 ± 0.0245	49	**0.024**
Specific C_{rs} ($L/cmH_2O/L$)	0.0295 ± 0.0162	57	0.0260 ± 0.0117	16	0.0352 ± 0.0331	42	0.287
IC (L)	1.24 ± 0.5865	63	1.59 ± 0.58	19	1.10 ± 0.62	44	**0.004**
ERV (L)	0.39 ± 0.33	63	0.62 ± 0.44	19	0.29 ± 0.20	44	**0.0001**
FRC (L)	1.39 ± 0.92	63	2.10 ± 1.10	19	1.09 ± 0.64	44	**<0.0001**
FRC (%pn)	44.9 ± 25.4	63	62.2 ± 26.5	19	37.4 ± 21.2	44	**0.0002**
RV (L)	1.01 ± 0.68	63	1.48 ± 0.71	19	0.80 ± 0.55	44	**0.0001**
RV (%pn)	52.9 ± 34.0	63	63.3 ± 25.6	10	48.4 ± 36.4	44	0.112
TLC (L)	2.64 ± 1.37	63	3.69 ± 1.48	19	2.19 ± 1.04	44	**<0.0001**
TLC (%pn)	45.2 ± 16.8	63	57.3 ± 16.2	19	40.0 ± 14.3	44	**0.0001**

Variable	All		MND		Other		*p*-value
IC % TLC	48.5 ± 13.9	63	44.2 ± 9.6	19	50.4 ± 15.1	44	0.103
ERV % TLC	13.9 ± 6.4	63	15.3 ± 7.1	19	13.3 ± 6.0	44	0.268
RV % TLC	37.4 ±14.6	63	40.5 ± 8.4	19	36.1 ± 16.4	44	0.269
RV/TLC (%pn)	111.9 ± 54.9	63	104.3 ± 29.5	19	115.1 ± 62.8	44	0.478
FRC % TLC	51.3 ± 13.9	63	55.8 ± 9.6	19	49.4 ± 15.0	44	0.093
FRC/TLC (%pn)	95.5 ± 27.2	63	98.8 ± 17.1	19	94.1 ± 30.6	44	0.530

Table 6-4: Respiratory function, for the cohort as a whole and by disease type sub-group

Data are presented as mean ± standard deviation, followed by "n" = the number of participants with technically acceptable measurements. Results were not obtainable in all due to bulbar impairment, technical issues or fatigue. *P*-values represent Student's independent two-sample *t*-test for comparison of means between MND and Other NMD sub-groups; data in **bold** indicate statistically significant values ($p<0.05$).

MND = motor neurone disease, Other = other neuromuscular diseases including chest wall disease, VC = vital capacity, PCF = Peak cough flow, MIP = Maximal inspiratory pressure, MEP = Maximal expiratory pressure, SNIP = Sniff nasal inspiratory pressure, C_{rs} = Total respiratory system compliance, Specific C_{rs} = C_{rs} divided by FRC, IC = Inspiratory capacity, ERV = Expiratory reserve volume, FRC = Functional residual capacity, RV = Residual volume, TLC = Total lung capacity, " volume% TLC" = lung volume variable expressed as a percentage of absolute TLC. %pn = percentage of predicted normal value.

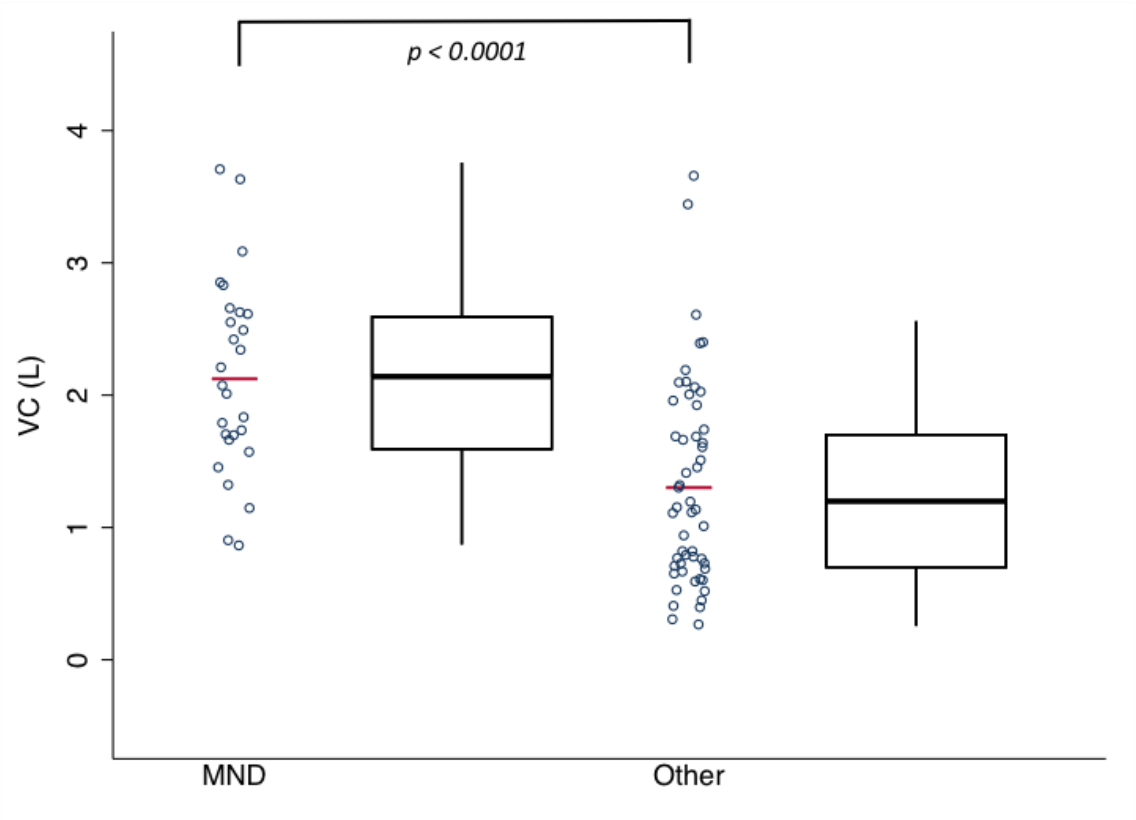

Figure 6-2: Vital capacity per participant, arranged by disease type

VC = vital capacity measured in litres, MND = motor neurone disease; Other = other neuromuscular diseases. Hollow circles represent individual participant data, red marker indicates sub-group mean. Box plot represents median, upper and lower quartiles; whiskers represent data within 1.5x IQR of these quartiles. *P*-value refers to Student's independent two-sample *t*-test for comparison of means.

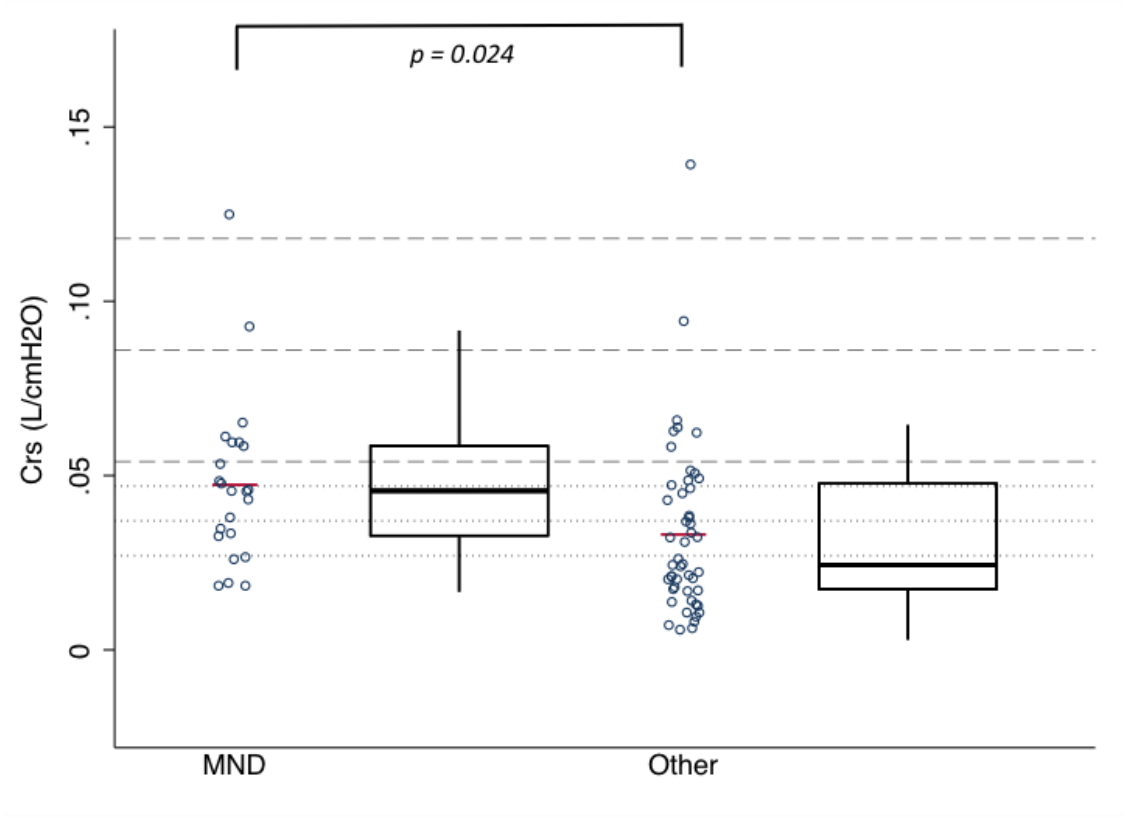

Figure 6-3: Respiratory system compliance per participant, arranged by disease type

Dashed reference lines refer to mean (±2 SD) values from Suratt (healthy control),[77] dotted reference lines refer to mean (±2 SD) values from Molgat-Seon (generalised NMD).[78]
C_{rs} = respiratory system compliance measured in litres per centimetres of water, MND = motor neurone disease; Other = other neuromuscular diseases. Hollow circles represent individual participant data, red marker indicates sub-group mean. Box plot represents median, upper and lower quartiles; whiskers represent data within 1.5x IQR of these quartiles. *P*-value refers to Student's independent two-sample *t*-test for comparison of means.

6.4.3 RELATIONSHIPS BETWEEN RESPIRATORY VARIABLES

Univariate associations between the response variables VC and PCF, and selected explanatory variables (age, gender, height, weight, disease type, MIP, MEP, SNIP, C_{rs}) are provided in Table 6-5. Statistically significant relationships were used in the multivariate regression modelling (tables depicting manual build in Appendix 11.3.3). The final multivariate regression models demonstrated that height and MEP were associated with VC in participants with MND (R^2=0.69, p<0.0001) (Table 11-5), whereas for participants in the Other NMD sub-group, VC was related to height and C_{rs} (R^2=0.36, p<0.0001) (**Table 11-7**). Post-hoc analyses were conducted with VC expressed as a percentage of predicted values, to account for sex, age, height and ethnicity (Appendix 11.3.3); these confirmed that MEP and C_{rs} were associated with VC in participants with MND and Other NMDs respectively. Peak cough flow was associated with IC alone in the MND sub-group (R^2=0.48, p=0.002), and VC, MEP and C_{rs} in participants with Other NMD (R^2=0.59, p<0.0001).

	Pearson's r *p*-value n	Age years	Height cm	Weight kg	VC L	IC L	ERV L	C_{rs} L/cmH_2O	MIP cmH_2O	MEP cmH_2O	SNIP cmH_2O
MND, N = 27	**VC L**	0.29 0.142 27	0.68 **0.0001** 27	0.19 0.335 27				0.70 **0.0002** 27	0.60 **0.002** 25	0.60 **0.004** 21	0.42 **0.033** 26
	PCF L/min	0.25 0.210 27	0.56 **0.002** 27	0.15 0.455 27	0.67 **0.0001** 27	0.68 **0.001** 19	0.58 **0.009** 19	0.62 **0.0015** 23	0.55 **0.005** 25	0.59 **0.004** 21	0.33 0.099 26
Other NMD, N = 53	**VC L**	0.37 **0.006** 53	0.62 **<0.0001** 53	0.53 **<0.0001** 53				0.54 **0.0001** 49	0.24 0.087 52	0.23 0.123 48	0.13 0.349 52
	PCF L/min	0.31 **0.026** 53	0.62 **<0.0001** 49	0.47 **0.0004** 53	0.64 **<0.0001** 53	0.63 **<0.0001** 44	0.31 **0.038** 44	0.20 0.167 49	0.19 0.188 52	0.40 **0.005** 48	0.25 0.075 52

Table 6-5: Univariate analysis of factors associated with vital capacity and peak cough flow, by disease type

Data in **bold** indicate statistically significant values ($p<0.05$)

N = total number of participants per sub-group. n = number of participants with paired measurements per correlation. MND = motor neurone disease; Other NMD = other neuromuscular disease including restrictive chest wall disease; VC = vital capacity; PCF = Peak cough flow; IC = Inspiratory capacity; ERV = Expiratory reserve volume; C_{rs} = Total respiratory system compliance; MIP = Maximal inspiratory pressure; MEP = Maximal expiratory pressure; SNIP = Sniff nasal inspiratory pressure.

6.4.4 RESPIRATORY TRACT INFECTIONS

Thirty-four participants reported at least one RTI in the year prior to study enrolment: 15 participants solely visited their primary-care practitioner, 13 attended hospital and 6 participants with multiple RTI episodes sought care from both health-care providers (Table 6-6). The overall incidence of RTI for this cohort of participants with NMD was 0.60 episodes/participant/year.

Six participants with MND reported a RTI compared to 28 participants in the Other NMD group (22% *vs.* 53% of respective sub-group, Fisher's exact test p=0.010) (Figure 6-4).

RTI Episode / year		Primary Care Presentation/s				
		0 episodes	1 episode	2 episodes	**Participant sub-total**	*Episode TOTAL*
Hospital Admission/s	0 episodes	**46**	11	4	**15**	*19*
	1 episode	12	4	0		*8 + 0*
	2 episodes	1	1	1		*3 + 4*
	Participant sub-total	**13**			**6**	
	Episode TOTAL	*14*				*48*

Table 6-6: Frequency of respiratory tract infections in the year prior to study enrolment, by episode type (primary-care or hospital)

Episodes were defined as respiratory symptoms requiring antibiotic use *and* RTI diagnosis made by a primary-care practitioner (general medical practitioner) or during a hospital inpatient admission.
Numbers represent number of individual participants with the corresponding episode type/s: diagonal shaded cell refers to 46 participants with zero RTI episodes; light grey shaded cells refer to participants who exclusively attended primary-care practitioner (n=15) or hospital (n=13) for their RTI episode/s. The remaining six participants attended a combination of primary-care and hospital for their multiple RTI episodes. Total number of participants = 80.
Total number of episodes = 48. Overall RTI incidence = 0.60/episodes/participant/year.

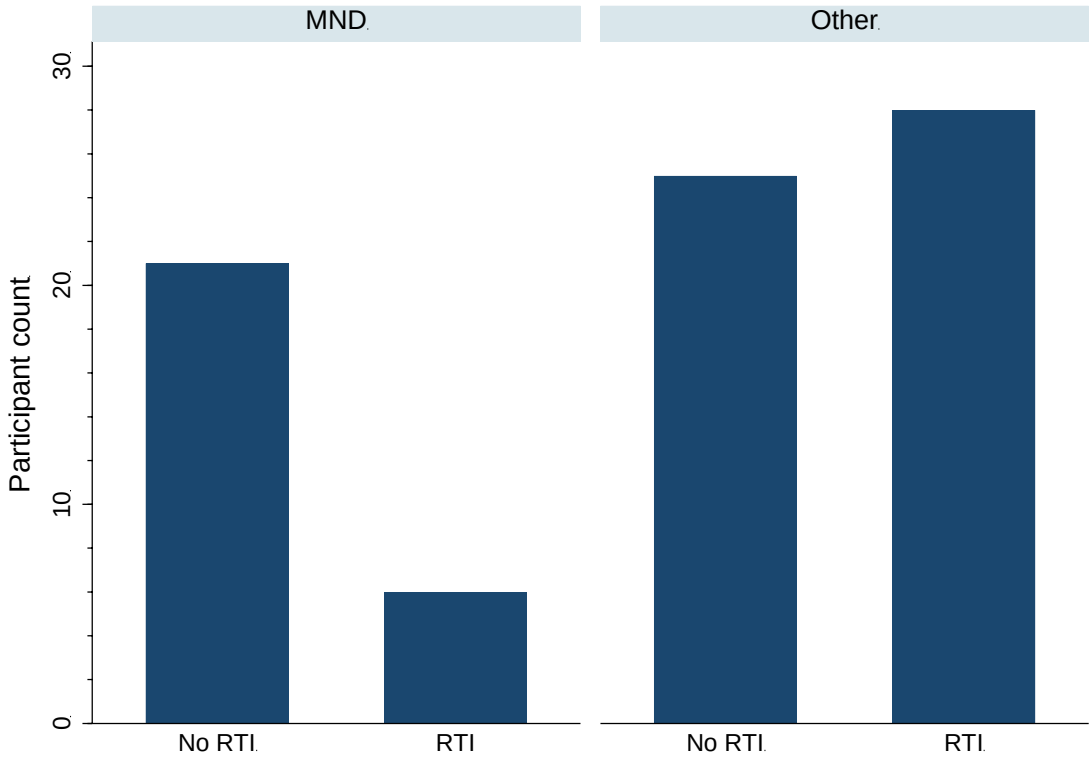

Figure 6-4: Incidence of respiratory tract infection in past year, by disease type

Fisher's exact test $p = 0.010$

MND = motor neurone disease, Other = other neuromuscular diseases including chest wall disease, RTI = self-reported respiratory tract infection in the preceding 12 months, No RTI = no episode of self-reported respiratory tract infection in the preceding 12 months.

Participants who experienced a RTI had lower VC, FRC, RV, TLC and PCF values (Table 6-7), however there were no differences in RTI rates when compartmental lung volumes were expressed as a percentage of the participant's individual TLC. Despite lower mean VC and PCF values overall in the group of participants with a RTI, there were no clear cut-off values that were associated with RTI history (Figure 6-5).

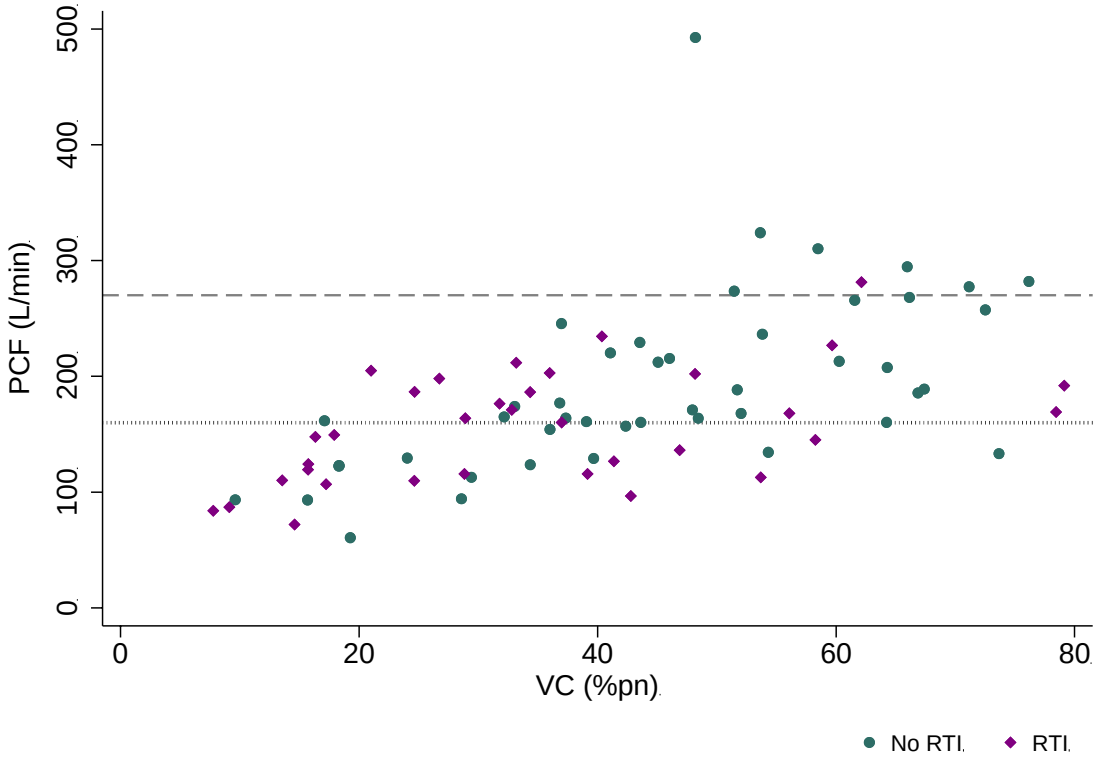

Figure 6-5: Vital capacity and peak cough flow, by past history of RTI

RTI = respiratory tract infection, VC = vital capacity, expressed as % of predicted normal value, PCF = peak cough flow measured in L/min. Dotted reference line indicates PCF value of 160 L/min, dashed reference line indicates PCF value of 270 L/min, as per published data[168,194] and incorporated into NMD management guidelines.[10-12,53,54,187]

Variable	No RTI		RTI		Mean difference (95% CI)	*p*-value
VC (L)	1.75 ± 0.83	46	1.35 ± 0.84	34	0.40 (0.02, 0.77)	**0.039**
VC (%pn)	45.6 ± 17.4	46	35.1 ± 18.7	34	10.5 (2.4, 18.6)	**0.012**
PCF (L/min)	192.9 ± 77.5	46	155.7 ± 48.9	34	37.2 (7.0, 67.3)	**0.016**
MIP (%pn)	42.3 ± 24.3	43	47.3 ± 27.5	34	-5.0 (-16.7, 6.8)	0.403
MEP (%pn)	41.8 ± 18.9	37	43.0 ± 25.3	32	-1.2 (-11.8, 9.5)	0.824
SNIP (%pn)	28.5 ± 15.6	44	26.6 ± 13.6	34	1.9 (-4.8, 8.6)	0.571
C_{rs} (L/cmH_2O)	0.0394 ± 0.0230	41	0.0354 ± 0.0280	31	0.0039 (-0.0080, 0.0159)	0.513
Specific C_{rs} (L/cmH_2O/L)	0.0259 ± 0.0147	33	0.0335 ± 0.0234	28	-0.0769 (-0.0175, 0.0022)	0.128
IC (L)	1.37 ± 0.64	34	1.10 ± 0.63	29	0.28 (-0.04, 0.60)	0.088
ERV (L)	0.43 ± 0.37	34	0.33 ± 0.27	29	0.10 (-0.07, 0.27)	0.237
FRC (%pn)	52.0 ± 28.4	34	36.6 ± 18.7	29	15.4 (3.0, 27.8)	**0.015**
RV (%pn)	61.3 ± 38.9	34	43.0 ± 24.3	29	18.4 (1.7, 35.0)	**0.032**
TLC (%pn)	50.8 ± 16.7	34	38.7 ± 14.6	29	12.0 (4.1, 20.0)	**0.004**
FRC % TLC	52.8 ± 12.5	34	49.7 ± 15.4	29	3.1 (-4.0, 10.1)	0.386
RV % TLC	39.3 ± 13.8	34	35.2 ± 15.3	29	4.1 (-3.3, 11.4)	0.273

Table 6-7: Respiratory function grouped by past history of respiratory tract infection

Data are presented as mean ± standard deviation, followed by "n" = the number of participants with technically acceptable measurements. Results were not obtainable in all due to bulbar impairment, technical issues or fatigue. *P*-values represent Student's independent two-sample *t*-test for comparison of means between No RTI and RTI sub-groups; data in **bold** indicate statistically significant values ($p<0.05$).

RTI = self-reported respiratory tract infection in the preceding 12 months, No RTI = no episode of self-reported respiratory tract infection in the preceding 12 months.VC = vital capacity, PCF = Peak cough flow, MIP = Maximal inspiratory pressure, MEP = Maximal expiratory pressure, SNIP = Sniff nasal inspiratory pressure, C_{rs} = respiratory system compliance, Specific C_{rs} = C_{rs} divided by FRC, IC = Inspiratory capacity, ERV = Expiratory reserve volume, FRC = Functional residual capacity, RV = Residual volume, TLC = Total lung capacity, “volume% TLC” = lung volume variable expressed as a percentage of absolute TLC.

The manual logistic regression build of factors associated with a past history of RTI in the previous year yielded a final model consisting of disease type and PCF (log likelihood = -48.2, χ^2 = 11.6, *p*=0.003). Vital capacity, C_{rs}, respiratory muscle strength and compartmental lung volumes were not significant variables (Appendix 11.3.4). Whilst PCF featured in the final model, increasing PCF had little effect on the odds of a prior RTI (OR = 0.99 (0.98, 1.00), standardised OR = 0.50 (0.25, 1.00)). In contrast, having Other NMD substantially increased the odds of reporting a RTI in the past year compared to participants with MND (odds ratio (OR) (95%CI) = 3.55 (1.20, 10.51)).

Receiver operating characteristic curves evaluating the sensitivity and specificity of published threshold values[168] to discriminate a past history of RTI are illustrated in Figure 6-6. People with Other NMDs only were included in these analyses, based on the multivariate model results above (and see Figure 6-4). Area under the curve values (AUC) (95% CI) were similar for both variables (VC = 0.62 (0.47, 0.77), PCF = 0.61 (0.45, 0.76)). Sensitivity and specificity applying a VC cut-off <1.1 L were 64% and 54% respectively, whilst a PCF threshold <160 L/min demonstrated 60% sensitivity and 50% specificity for identifying participants with a past history of RTI.

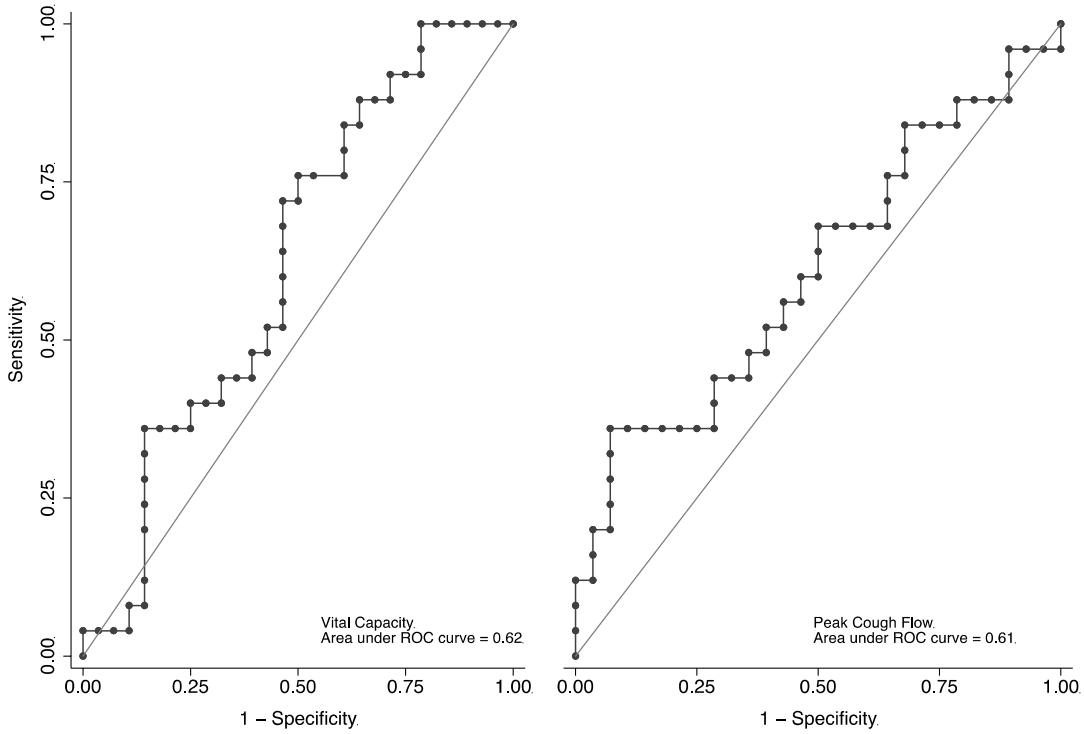

Figure 6-6: ROC curves for past history of RTI, for vital capacity (left) and peak cough flow (right)

ROC = Receiver operating characteristic, RTI = respiratory tract infection

6.5 DISCUSSION

The eighty community-dwelling, medically-stable participants with neuromuscular or restrictive chest wall disease in this cross-sectional study represent a cohort with severe respiratory muscle weakness and lung volume restriction. A third were diagnosed with MND and had lived with symptoms for approximately two years, starting at a median age of 64 years. The remaining participants had various forms of Other NMDs, with muscular dystrophies, spinal muscular atrophy and primary restrictive chest wall disease comprising the largest diagnostic groups. The Other NMD sub-group had symptoms spanning over two decades, commencing at a median age of 26 years. These participants were younger and shorter than those with MND, reflecting the predominantly childhood onset and likely growth impairment associated with their conditions.

In keeping with the degree of ventilatory restriction, two-thirds of the population were nocturnal NIV-users. A further 10% used NIV during the daytime as well (Table 6-3). The majority of participants reported not performing respiratory therapy (78%) nor cough augmentation techniques (91%). This figure was consistent with the broader population they were recruited from; although routine use of LVR or mechanical insufflation were study exclusion criterion, only 7 of 128 potential participants (5%) were excluded on this basis.

6.5.1 RESPIRATORY FUNCTION BETWEEN DISEASE TYPES

The heterogeneity of this large group revealed important differences in underlying respiratory function between disease sub-groups. Participants with MND were at a similar stage of disease progression in terms of requiring domiciliary ventilatory support (74% compared to 79% of Other NMD), however they had larger IC, ERV and therefore VC values compared to participants with Other NMD. Severity of respiratory muscle weakness was similar between the sub-groups, and therefore weakness alone does not explain the discrepancy in loss of lung capacity. Total respiratory system

compliance was lower in participants with Other NMD and is a plausible partial causative mechanism for the difference.

Supporting this hypothesis, VC was related to height and MEP in the MND sub-group, whereas height and C_{rs} were the significant factors in participants with Other NMD. The presence of height in the models is expected, as analyses were performed on VC as an absolute value in litres, and height is known to influence lung capacity.[244] When the model was re-run using percentage of predicted values, which take into account an individual's sex, age, height and ethnicity, height was absent yet MEP remained for participants with MND, as did C_{rs} for Other NMDs (Appendix 11.3.3).

The weak relationship between inspiratory muscle strength and VC in participants with Other NMD, using either absolute or percentage predicted values, was unexpected. Previous literature has demonstrated a curvilinear relationship between VC and respiratory muscle strength in the healthy population,[288] and some authors have shown a quasi-linear relationship in people with NMD.[147,171] This contrast with previous literature may signify a chance finding or may potentially reflect the severity of our population or time living with disease; muscle strength may be strongly related to VC when respiratory system recoil is normal, but in the context of significant pathology such as chest wall stiffness or deformity, normal assumptions regarding respiratory forces and mechanics may not apply. It has previously been observed that lung volume loss in people with NMD is more than that expected for the degree of muscle weakness alone, and authors have hypothesised that "fixed restriction" may limit VC more than muscle strength in some people with a NMD.[143,147,149,152] De Troyer[147] and Estenne[152] postulated that chest wall and lung compliance were involved, however few studies since have measured C_{CW}, C_L or C_{rs} in people with NMD. Recently, a study of 12 people with slowly-progressive NMD found a relationship between VC and C_{rs} (r=0.65, p<0.05).[78] Our study confirms this association in a larger group and corroborates the hypothesis that respiratory system stiffness is an important characteristic of slowly-progressive NMD.

In contrast, in people with rapidly-progressive disease such as MND, we speculate loss of lung volume may be more closely associated with respiratory muscle strength alone,

at least initially. In this current study, this sub-group more closely followed the respiratory physiology observed in healthy subjects,[288] whereby height and respiratory muscle strength (in this case MEP r^2=0.69) rather than C_{rs} were associated with VC. Respiratory system compliance was reduced in participants with MND (sub-group mean 0.0473 ± 0.0241 L/cmH_2O) compared to values obtained in healthy volunteers using similar C_{rs} measurement techniques (0.086 ± 0.016 L/cmH_2O[77]), but not to the extent seen in those participants with Other NMD (sub-group mean 0.0331 ± 0.0245 L/cmH_2O). Supporting the theory that respiratory muscle dysfunction is likely an early contributor to loss of lung volume, histological samples from people living with MND demonstrate significant diaphragm atrophy and compensatory fibre-type remodelling, despite only moderate impairment of VC.[289] We therefore postulate that people with NMD start with weakness and then develop a rigid chest wall and/or lung tissue over time.

Although C_{rs} was lower in participants with Other NMDs compared to MND, specific C_{rs} was comparable. Specific compliance (compliance divided by lung volume, either TLC or FRC) normalises for differences in lung size, an important consideration when analysing C_L, as the pressure-volume relationship of the lungs is influenced by lung volume.[73,265] This phenomenon is apparent when comparing adults and children: for the equivalent pressure change, the *absolute* volume change in a child's lungs will be smaller than an adult and C_L lower, despite similar elastic characteristics of the lung tissue. Once normalised for total lung volume however, specific C_L is comparable between children and adults.

Similarly, it is important to interpret C_L in conjunction with lung volume and specific C_L, as demonstrated by De Troyer and colleagues in a study of people with tetraplegia. In isolation, low C_L may be attributable to a change in lung tissue elasticity. However after considering lung volume and specific C_L, they concluded that alveolar collapse could explain the reduction in C_L, with the remaining ventilated alveoli retaining normal elastic properties.[66,147]

Whilst the example above illustrates the value of specific C_L, there is little information published about specific C_{rs}. Whether there is a similar dependency between lung size

and the pressure-volume relationship of the chest wall or respiratory system as a whole is unclear. It has previously been demonstrated that restriction of the chest wall in control participants by chest wall strapping reduces C_L and C_{CW}, hence C_{rs}. Importantly, the decline in C_{CW} was primarily responsible for the substantial fall in FRC observed with increasing restriction.[150] When calculated (using published data and Section 2.3.3, Equation 2), specific C_L did not change from the normal to strapped state, as expected given lung tissue remained healthy. However only a very mild reduction was identified in specific C_{CW} and specific C_{rs} implying near-normal elastic behaviour, despite the chest wall being tightly bound. Interpretation of specific C_{CW} or specific C_{rs} may not necessarily follow the principles of specific C_L, particularly if reduced distensibility of the extra-thoracic respiratory system is responsible for the loss of lung volume that we are normalising for.

A limitation of the compliance measure employed in this study is that it cannot distinguish between the relative contributions of C_L versus C_{CW}. Invasive measurements, made using an oesophageal balloon and a technique that requires considerable participant training, are required to measure C_L (and hence mathematically calculate C_{CW} from C_{rs}) in spontaneously breathing individuals. Given our cohort's level of functional and respiratory disability, we were concerned that such assessments would be poorly tolerated, potentially negatively impacting on recruitment and retention. As such we decided against invasive measures of C_{CW} or C_L.

As anticipated, TLC and compartmental lung volumes were also reduced compared to predicted normal values. Again, differences were noted between disease types, with participants with MND having better preserved IC, ERV, FRC, RV and TLC. However when these components were expressed as a percentage of TLC, no between-group differences were found, implying that lung volume was smaller overall in the sub-group of people with Other NMDs, rather than any selective reduction in IC or increase in RV as has previously been noted in some people with slowly-progressive NMDs.[146,149,152] The FRC%TLC and RV%TLC ratios fell within the range of normal predicted values, further supporting the conclusion that global rather than isolated or selective respiratory restriction is present in people with NMD.

The group mean decrease in RV observed in this study contrasts with previous data suggesting that RV is increased in NMD. These previous studies were small,[143] or comprised predominantly of people with combined inspiratory and expiratory muscle weakness[146,149,152] Normal RV values have been reported in participants with predominantly inspiratory muscle weakness[146] or more severe restriction,[78,147] whereas a study of 155 people with NMD reported low FRC and ERV values with considerable variance.[109] The large range of static lung volume values seen in our data and by others suggests that change in RV in particular may not be as uniform as previously suspected, likely due in part to the heterogeneity of respiratory muscles affected in NMD, and the aforementioned influence of C_{rs} affecting respiratory mechanics.

6.5.2 PEAK COUGH FLOW

Despite differences in lung capacity, we found PCF to be similar between participants with MND and Other NMD. Height, lung volumes (VC, IC, ERV), muscle strength and C_{rs} were all associated with PCF on univariate analysis in the MND sub-group, with IC being the predominant factor on multivariate regression. In participants with Other NMD, the respiratory variables VC, MEP and C_{rs} were related to the PCF produced.

The current findings of higher lung volumes and MEP being related to PCF is consistent with other literature[100,168,171] and supports the notion that strategies to improve these components may increase PCF.[109] Although assisting inflation and then coughing is well-established as a method to improve PCF, it should be highlighted that the association between PCF and lung volumes found in this and other studies is with VC or IC measured during a separate maximal manoeuvre.

As with prior research, we did not investigate the effect of the spontaneous pre-cough inspiratory capacity on PCF. One study has demonstrated that assisting inspiration to a sub-maximal volume produces a higher assisted PCF than a maximal pre-cough inspiration in participants with NMD.[99] In healthy participants, incremental increases in the operating volume of voluntary coughs improved PCF, however gastric,

oesophageal and trans-diaphragmatic pressures did not change significantly.[88] This work also suggests that changes in PCF may not reflect cough mechanics or driving pressures, the underlying physiological basis of cough. More research investigating whether the size of the spontaneous breath immediately prior to coughing correlates to unassisted PCF, other cough metrics or airway clearance in participants with NMD is required.

Uniquely, this is the first study that has included C_{rs} in PCF modelling. Theoretically when compliance is reduced, more passive elastic recoil is stored in the lungs and chest wall, thereby increasing P_A, promoting dynamic airway compression and the generation of higher expiratory flows. A meta-analysis of respiratory muscle training postulated that improving IC and thus static recoil pressure may be the mechanism by which MEP increases in people with SCI and absent or diminished abdominal muscle activity.[203] Our findings are consistent with this hypothesis; in addition to lung volume and expiratory muscle strength, the stiffer respiratory system associated with NMD was a factor influencing PCF and may play a beneficial role during cough.

A limitation of this PCF modelling is that we did not include bulbar impairment in our analysis. Transient glottic closure builds up P_A during the compressive phase of cough,[81,88] therefore it follows that bulbar dysfunction may impact on the resultant expiratory flow. Impaired bulbar function was present in 44% of participants with MND, as indicated by the ALSFRS-R bulbar sub-score,[287] however a larger study with greater variation in PCF and glottic function would be necessary to meaningfully evaluate this relationship. Likewise, although PCF is being increasingly used in bulbar assessment,[119,290] and poor bulbar function in participants with MND is strongly associated with an inability to clear secretions during acute respiratory infection,[111] further research is required to better understand the interplay between bulbar dysfunction, PCF (or other cough metrics), airway protection and airway clearance.

6.5.3 RESPIRATORY TRACT INFECTIONS

The clinical significance of poor lung volumes and cough is thought to be an increased risk of RTI. In this sample of community-dwelling people with NMD, 43% reported at least one RTI resulting in antibiotic treatment within the previous year, with an incidence of 0.60 episodes/participant/year. Participants with Other NMD were 3.5 times more likely to report a prior episode than those with MND.

Participants who had experienced a RTI had smaller lung capacity and PCF than those who had no RTI, however respiratory muscle strength and C_{rs} were comparable. Although PCF and VC were statistically lower, there was considerable overlap of values amongst participants in the two RTI categories (Figure 6-5). Ninety percent of people in this cohort had a PCF value <270 L/min, the level at which one is reported to be at risk of developing a RTI,[194] however less than half the group reported a RTI in the preceding 12 months. Additionally, respiratory variables did not feature in the logistic regression model of factors associated with having a past episode, suggesting that whilst moderate to severely impaired respiratory function was common in this population, it did not distinguish between participants who had a RTI and those who had not. In the current study, respiratory function was measured after the RTI; whether it was lower prior to the RTI and potentially a causative factor versus lower as a result of the RTI cannot be distinguished from a cross-sectional design such as this.

The event rate of past history of RTI in this study is similar to reports in DMD[167] and a paediatric NMD cohort.[168] However, our rate of 22% in participants with MND was much lower than the 75% observed in a prospective year-long study,[111] despite our sample having substantially lower VC, MIP, MEP and PCF. The retrospective, self-reported measure adopted herein may lead to under-estimation of episodes, however our definition of a RTI was broad and we contacted health-care providers if participants could not recall their past history. The majority of our MND cohort used NIV (74%) and had a gastrostomy in situ (63%), although they did not practice cough augmentation strategies (93%). In Sancho and colleagues' study, all were trained to use cough augmentation techniques, but NIV or gastrostomy use were unreported.[111]

Local health service model and access to multidisciplinary care improves survival in MND,[291] therefore variations in general and respiratory care between the two study centres may have contributed to differences in RTI rates.

Moreover, disparity in bulbar function is likely to be a considerable factor; 44% of the current cohort had moderate dysfunction, defined as an ALSFRS-R bulbar sub-score ≤9,[287] whereas Sancho *et al* reported that 73% had signs of bulbar dysfunction (mean Norris bulbar scale = 18.9 ± 6.9).[111] Although our group had worse respiratory function, we speculate that the relative preservation of their bulbar muscles enabled sufficient P_{pl} generation during cough for effective airway clearance and airway protection. Conversely, poor glottic function in the context of only moderately impaired lung volume restriction (mean FVC = 59% predicted)[111] may result in a higher proportion of participants with an ineffective cough, thereby predisposing them to RTIs. Whilst intuitively measures such as PCF, lung volumes or muscle strength seem linked to RTI episodes, the multifaceted nature of respiratory complications in people with NMD may mean that the relationship is not as simple as presumed.

The ability to predict which patients are at risk of developing a RTI and therefore target management to prevent this occurrence is clearly desirable in a population whose primary cause of discomfort and death is of a respiratory nature. In fact, the study by Sancho and colleagues above is a rare example of a prospective study investigating factors when well that could then identify patients unable of clearing secretions during a RTI.[111] The most commonly cited PCF[103,194] and/or FVC[168] cut-offs however come from retrospective or small cross-sectional studies. As discussed previously, these source data are imperfect, nonetheless these values (PCF <270 L/min or VC <1.1 L) are widely cited and interpreted as representing risk of respiratory complication or hospitalisation.[53] Applying these thresholds to the current cohort, they demonstrated poor diagnostic ability (sensitivity 60-64%, specificity 50-54%) in identifying participants who had a RTI in the preceding year. Our data highlight the need for a longitudinal study to find sensitive markers that *predict* who may be at risk of developing a RTI in the future. Examining whether cut-offs can *differentiate* participants who had a RTI in the past is an initial step on this path.

6.6 CONCLUSION

In this cohort of 80 community-dwelling people with NMD and respiratory system involvement there were significant differences between participants with MND and other, generally more slowly-progressive forms of NMD. Participants with Other NMD had smaller lung volumes, lower C_{rs} and higher incidence of RTI in the previous year compared to those with MND disease. Respiratory muscle strength and PCF were similar between the two groups. Greater impairment of lung volume was seen in all lung capacities and volumes (i.e., IC, ERV, VC, FRC, RV), such that both diseases demonstrated similar reductions in compartmental lung volumes once this overall loss of TLC was taken into account.

Participants with Other NMDs, most of who had lived with their condition for more than a decade, demonstrated a relationship between VC and C_{rs}. Notably, respiratory muscle strength was not associated with VC in this sub-group. In contrast, VC was significantly related to MEP in the MND sub-group, as was C_{rs} on univariate analysis. We therefore speculate that respiratory muscle strength is an early factor related to loss of lung volume in people with MND, however the observation that VC and C_{rs} are interrelated particularly in more long-standing disease does suggest a pathway that is potentially modifiable.

The likelihood of participants having had a RTI in the year prior to this study was higher for those with Other NMD. Whilst lung volumes and PCF were lower in those participants who reported a prior event, these measures were not sensitive or specific enough to accurately distinguish who had experienced a RTI. A longitudinal study design measuring respiratory and bulbar function, along with respiratory management in people with NMDs is needed to establish causality between impaired respiratory function and incidence of RTI. Such a study would also help to identify RTI risk factors and identify who may benefit from intervention to optimise long-term respiratory function.

7 PRE-POST INTERVENTION STUDY: IMMEDIATE EFFECTS OF LVR

7.1 INTRODUCTION

Given the findings of the previous chapter of low lung volumes and C_{rs} in participants with NMDs, and known relationships between VC and clinical outcomes such as hypercapnia, respiratory failure and need for nocturnal ventilation, there exists a plausible rationale for performing therapies that augment lung volume. Lung volume recruitment is one such technique, however there is a paucity of studies evaluating the short-term effects of LVR. Thus there are two aims of this chapter; the first is to describe the proportion of participants, naïve to regular LVR, who can perform the technique and explore characteristics between those who are able to achieve a LIC greater than spontaneous VC, and those who cannot. The second is to investigate the immediate physiological effects of performing a single-session of LVR on respiratory function in naïve participants.

7.2 NULL HYPOTHESES

1. That this cohort of people living with NMD will not be able to perform LVR successfully, defined as achieving a LIC greater than 10% above their VC.
2. That a single-session of LVR will not change respiratory function, specifically C_{rs}, LIC and static lung volumes.

7.3 METHODS

A prospective pre-post intervention study was conducted during the research project's initial assessment session (Timepoint 0) (Table 7-1).

The baseline assessment conducted at Timepoint 0a (T0a) constituted the pre-session assessment. After a 45-minute rest period a standardised LVR session was performed, followed immediately by re-assessment of respiratory function measures (Timepoint 0b, T0b). The LVR session comprised two sets of five maximal inflations, performed using a LVR kit with mouthpiece and nose clip, or oro-nasal mask if the mouthpiece leaked. The number of compressions required to reach LIC was individualised to each participant. All treatment was performed by the same clinician.

Ability to perform LVR successfully ("recruitable") was defined as achieving a LIC at least 10% greater than VC ((LIC minus VC difference / VC) multiplied by 100) >10%) during either Timepoint 0a or Timepoint 0b testing session/s.

Table 7-1 summarises the outcomes measured, which were defined in Section 3.6. Equipment, procedures and measurement methods were detailed in Chapters 4 and 5.

Statistical analysis was detailed in Chapter 3, with C_{rs} selected as the primary outcome to evaluate the immediate effect of LVR. Linear mixed models were also constructed using secondary outcomes (LIC, static lung volumes, VC, specific C_{rs}, PCF) as the response variable, disease type (MND/Other) and time (T0a/T0b) as fixed effects, and person as a random effect.

	Timepoint 0a	Timepoint 0b	Timepoint 1	Timepoint 2	Timepoint 3a	Timepoint 3b
Time	Time 0, Ax (a)	Time 0, Ax (b)	1-month	2-month	3-month, Ax (a)	3-month, Ax (b)
Location	Austin Health		Participant's Home	Participant's Home	Austin Health	
Duration	5-6 hours		2-3 hours	2-3 hours	5-6 hours	
Measures						
Demographic information	✓				✓	
Respiratory information	✓				✓	
VC	✓	✓	✓	✓	✓	✓
PCF	✓	✓	✓	✓	✓	✓
FVC, FEV_1	✓				✓	
MIP, MEP, SNIP	✓				✓	
Static lung volumes	✓	✓	✓	✓	✓	✓
C_{rs}	✓	✓	✓	✓	✓	✓
LIC	✓	✓	✓	✓	✓	✓
PCF_{LIC}	✓	✓	✓	✓	✓	✓
SRI	✓				✓	
AQoL-8D	✓				✓	
ALSFRS-R	✓ if MND				✓ if MND	
Other		Randomised Training session	Treatment review	Treatment review		Treatment review Usual care session

Table 7-1: Schedule of data collection: Pre-post intervention study

Shaded cells represent components applicable to this sub-study. Ax (a) = pre-session assessment, Ax (b) = post-session assessment. VC = vital capacity, PCF = peak cough flow, FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 second, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure, SNIP = sniff nasal inspiratory pressure, C_{rs} = respiratory system compliance, LIC = lung insufflation capacity, PCF_{LIC} = peak cough flow from lung insufflation capacity. SRI = Severe Respiratory Insufficiency questionnaire, AQoL-8D = Assessment of Quality of Life questionnaire, ALSFRS-R = Revised Amyotrophic Lateral Sclerosis Functional Rating Scale, MND = motor neurone disease.

7.4 RESULTS

7.4.1 PARTICIPANTS

Eighty consecutive participants were recruited. Demographic details were provided in Chapter 6.

7.4.2 ABILITY TO PERFORM LVR, EFFECT ON VOLUME AND PCF DURING MANOEUVRE

Sixty-one participants (76%) achieved a LIC – VC difference >10% of VC during Timepoint 0a. Of the remaining 19 participants, 15 obtained this criterion after the LVR session. Four males (mean ± SD age = 69.8 ± 5.0 years), diagnosed with MND (2), PLS (1), and myotonic dystrophy (1) were not recruitable at either timepoint. Given this small number, further investigation of differences between people who could and couldn't successfully increase LIC above VC with LVR was not undertaken.

The 25 participants with MND who could perform LVR had an ALSFRS-R summary score of 24.1 ± 7.2, and a bulbar sub-score of 8.8 ± 3.5 points. Eleven participants had a bulbar sub-score ≤9 indicating moderate bulbar symptoms.[287]

Group mean LIC was 25% higher than VC (1.97 ± 1.02 L *vs.* 1.58 ± 0.85 L, paired *t*-test $p<0.0001$). People with MND had higher absolute VC and LIC than those with Other NMDs (Figure 7-1), however there was no difference in the additional volume recruited (LIC – VC), either absolute (L) or expressed as a percentage increase from VC (%VC) (Table 7-2). Overall, there was no increase in PCF with the addition of LVR (PCF_{LIC} = 174.9 ± 56.6 L/min *vs.* PCF = 177.1 ± 69.0 L/min, paired *t*-test $p=0.711$), nor any difference in PCF_{LIC} or PCF_{LIC} – PCF difference between people with MND and Other NMDs (Table 7-2, Figures in Appendix 11.3.5). Between-group differences in other baseline respiratory parameters, including VC and PCF, were presented in Chapter 6.

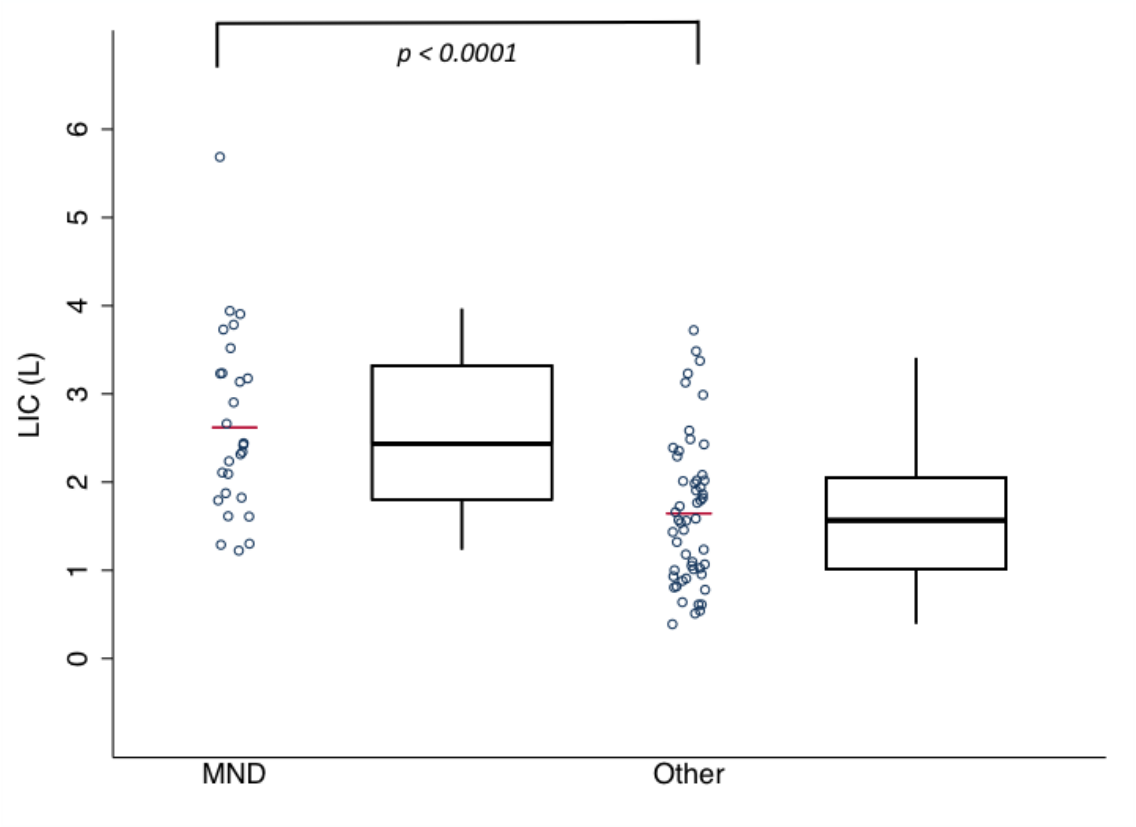

Figure 7-1: Lung insufflation capacity per participant, arranged by disease type

LIC = lung insufflation capacity measured in litres at Timepoint 0a
MND = motor neurone disease; Other = other neuromuscular diseases. Hollow circles represent individual participant data, red marker indicates sub-group mean. Box plot represents median, upper and lower quartiles; whiskers represent data within 1.5x IQR of these quartiles. *P*-value refers to Student's independent two-sample *t*-test for comparison of means.

Variable	All (n = 80)	MND, mean±SD (n = 27)	Other, mean±SD (n = 53)	*p*-value
VC (L)	1.58 ± 0.85	2.12 ± 0.75	1.30 ± 0.77	**<0.0001**
VC (%pn)	41.1 ± 18.6	53.1 ± 15.4	35.0 ± 17.2	**<0.0001**
LIC (L)	1.97 ± 1.02	2.62 ± 1.05	1.65 ± 0.83	**<0.0001**
LIC – VC (L)	0.40 ± 0.53	0.49 ± 0.66	0.35 ± 0.44	0.233
LIC – VC (%VC)	0.3 ± 0.5	26.0 ± 32.4	39.5 ± 52.0	0.222
PCF (L/min)	177.1 ± 69.0	187.4 ± 61.3	171.9 ± 72.6	0.346
PCF_{LIC} (L/min)	174.9 ± 56.6	191.7 ± 65.3	166.4 ± 50.2	0.059
PCF_{LIC} – PCF (L/min)	-2.2 ± 52.0	4.3 ± 42.3	-5.5 ± 56.3	0.429

Table 7-2: Respiratory function at Timepoint 0a

(n) = the number of participants with technically acceptable measurements. Results were not obtainable in all due to bulbar impairment, technical issues or fatigue. *P*-value represents Student's independent two-sample *t*-test for comparison of means between MND and Other NMD sub-groups; data in **bold** indicate statistically significant values ($p<0.05$).

MND = motor neurone disease, Other = other neuromuscular diseases including chest wall disease, VC = Vital capacity, LIC = Lung insufflation capacity, LIC – VC = LIC minus VC difference, PCF = Peak cough flow, PCF_{LIC} = PCF from LIC, PCF_{LIC} – PCF = PCF_{LIC} minus PCF difference.

%pn = percentage of predicted normal, %VC = value expressed as percentage of baseline VC.

7.4.3 Immediate Effect of LVR on Respiratory Function in a Naïve Population

Summary data of the immediate effect of LVR on respiratory function in this naïve population of participants with heterogeneous NMD are provided in Table 7-3 (disease sub-groups in Appendix 11.4). Pairwise comparisons for the cohort as a whole suggested statistically significant improvements in LIC, LIC – VC difference, C_{rs}, specific C_{rs}, PCF_{LIC} and the PCF_{LIC} – PCF difference over time (Δ at Time 0 = Timepoint 0b minus 0a).

Variable	n	Timepoint 0a mean±SD	Timepoint 0b mean±SD	Δ at Time 0 Mean difference (95% CI)	*p*-value
LIC (L)	78	1.99 ± 1.02	2.12 ± 1.07	0.13 (0.05, 0.21)	**0.002**
VC (L)	78	1.57 ± 0.86	1.54 ± 0.84	-0.03 (-0.07, 0.01)	0.142
LIC – VC (L)	78	0.42 ± 0.50	0.57 ± 0.43	9.4 (2.9, 15.8)	**0.0003**
LIC – VC (%VC)	78	36.5 ± 45.9	45.9 ± 43.8	0.16 (0.07, 0.24)	**0.005**
C_{rs} (L/cmH_2O)	65	0.0377 ± 0.0258	0.0415 ± 0.0270	0.0038 (0.0001, 0.0075)	**0.047**
Specific C_{rs} (L/cmH_2O/L)	44	0.0316 ± 0.0174	0.0356 ± 0.0219	0.0041 (0.0011, 0.0070)	**0.008**
FRC (L)	49	1.39 ± 0.98	1.36 ± 0.97	-0.03 (-0.09, 0.03)	0.348
TLC (L)	49	2.64 ± 1.45	2.60 ± 1.41	-0.03 (-0.10, 0.03)	0.266
RV (L)	49	1.00 ± 0.73	0.99 ± 0.71	-0.02 (-0.07, 0.04)	0.610
ERV (L)	49	0.38 ± 0.32	0.37 ± 0.34	-0.01 (-0.05, 0.02)	0.435
IC (L)	49	1.24 ± 0.70	1.25 ± 0.67	0.00 (-0.04, 0.04)	0.890
PCF (L/min)	78	175.5 ± 69.1	169.9 ± 57.6	-5.6 (-15.0, 3.9)	0.244
PCF_{LIC} (L/min)	77	174.8 ± 56.7	186.4 ± 57.9	11.6 (3.7, 19.5)	**0.005**
PCF_{LIC} – PCF	77	-1.5 ± 51.9	15.7 ± 39.5	17.2 (4.2, 30.2)	**0.010**

Table 7-3: Summary data of the immediate effect of LVR on respiratory function

Total number of participants who completed assessments at Timepoint 0a and 0b = 78. Δ at Time 0 = Timepoint 0b minus 0a
(n) = the number of participants with technically acceptable measurements at both timepoints. Results were not obtainable in all due to bulbar impairment, technical issues or fatigue. *P*-value represents paired *t*-test comparison (Timepoint 0b minus 0a); data in **bold** indicate statistically significant values ($p<0.05$).

LIC = lung insufflation capacity, VC = vital capacity, LIC – VC = LIC minus VC difference, C_{rs} = Total respiratory system compliance, Specific C_{rs} = C_{rs} divided by FRC, FRC = Functional residual capacity, TLC = Total lung capacity, RV = Residual volume, ERV = Expiratory reserve volume, IC = Inspiratory capacity, PCF = Peak cough flow, PCF_{LIC} = PCF from LIC, PCF_{LIC} –PCF = PCF_{LIC} minus PCF difference.

The linear mixed models confirmed this main effect of time on LIC, LIC – VC, C_{rs}, specific C_{rs}, PCF_{LIC} and PCF_{LIC} – PCF (Table 7-4). Both MND and Other NMDs improved LIC following the single-session of LVR (Figure 7-2); the observed mean (95% CI) magnitude of 0.12 (0.05, 0.18) L was statistically significant for the Other disease group (p=0.0005), whereas the 0.15 (-0.06, 0.36) L change in the MND group was not (p=0.151). No between-group difference was identified (p=0.670).

Similarly, the improvement in LIC – VC difference, specific C_{rs}, PCF_{LIC} and PCF_{LIC} – PCF over time appeared to be predominantly in participants with Other NMDs, although no between-group differences were noted (Table 7-5).

Main effects of disease were found for LIC, C_{rs} and the lung volumes VC, IC, ERV, FRC, RV and TLC (Table 7-4). Post-hoc comparisons of the observed data for all these variables demonstrated statistically significant lower values in people with Other NMDs compared to MND, at both timepoints (Appendix 11.4.2). These data confirm the differences in respiratory function between people with MND and Other NMDs described in Chapter 6. No effects of disease or time were seen on PCF, and the overall model was not statistically significant (p=0.070).

Disease by time interaction effects were observed for C_{rs} (Figure 7-3), FRC (Figure 7-4), RV and TLC. Post-hoc analysis suggested that participants with MND improved C_{rs} more so than those people with Other NMD (Table 7-5; between-group difference p=0.008). In the smaller sub-set of participants with nitrogen washout measurement of lung volumes, FRC and TLC fell in the MND group following a single-session of LVR. No change was seen in Other NMDs, hence between-group differences were present (Table 7-5).

Variable model		χ^2	*p*-value
LIC model log restricted likelihood = -139.9		***31.5***	***<0.0001***
	Time	10.30	**0.001**
	Disease	20.87	**<0.0001**
	Interaction	0.20	0.654
VC model = -68.8		***23.7***	***<0.0001***
	Time	2.90	0.088
	Disease	20.60	**<0.0001**
	Interaction	0.81	0.367
LIC – VC model = -87.9		***18.9***	***0.0003***
	Time	15.58	**0.0001**
	Disease	3.04	0.081
	Interaction	0.63	0.428
C_{rs} model = 350.4		***22.3***	***0.0001***
	Time	9.38	**0.002**
	Disease	10.04	**0.002**
	Interaction	7.69	**0.006**
Specific C_{rs} model = 254.3		***9.1***	***0.028***
	Time	4.03	**0.045**
	Disease	1.60	0.207
	Interaction	0.22	0.643
FRC model = -73.5		***25.1***	***<0.0001***
	Time	3.97	**0.046**
	Disease	18.00	**<0.0001**
	Interaction	4.93	**0.026**
TLC model = -96.1		***28.9***	***<0.0001***
	Time	6.11	**0.013**
	Disease	18.85	**<0.0001**
	Interaction	7.59	**0.006**
RV model = -53.1		***20.0***	***0.0002***
	Time	2.47	0.116
	Disease	13.74	**0.0002**
	Interaction	4.71	**0.030**

Variable model	χ^2	*p*-value
ERV model = 11.6	***17.2***	***0.0007***
Time	0.44	0.507
Disease	16.21	**0.0001**
Interaction	0.02	0.885
IC model = -37.0	***9.1***	***0.028***
Time	0.09	0.767
Disease	8.04	**0.005**
Interaction	0.75	0.388
PCF model = -827.5	*7.1*	*0.070*
Time	0.41	0.520
Disease	2.82	0.093
Interaction	2.70	0.100
PCF_{LIC} model = -801.6	***12.3***	***0.006***
Time	6.02	**0.014**
Disease	2.77	0.096
Interaction	0.93	0.335
PCF_{LIC} – PCF model = -808.2	***11.2***	***0.011***
Time	4.06	**0.044**
Disease	0.10	0.749
Interaction	3.45	0.063

Table 7-4: Linear mixed models of effect of Time and Disease on respiratory function in participants with neuromuscular disease, naïve to LVR

Time represents pre (Time 0a) and post (Time 0b) a single-session of LVR; Disease signifies motor neurone disease or other neuromuscular disease; where Time and Disease are fixed effects and participant a random effect. *P*-values in **bold** indicate statistically significant values ($p<0.05$).

LIC = lung insufflation capacity, C_{rs} = Total respiratory system compliance, Specific C_{rs} = C_{rs} divided by FRC, VC = vital capacity, LIC – VC = LIC minus VC difference, FRC = Functional residual capacity, TLC = Total lung capacity, RV = Residual volume, ERV = Expiratory reserve volume, IC = Inspiratory capacity, PCF = Peak cough flow, PCF_{LIC} = PCF from LIC, PCF_{LIC} –PCF = PCF_{LIC} minus PCF difference.

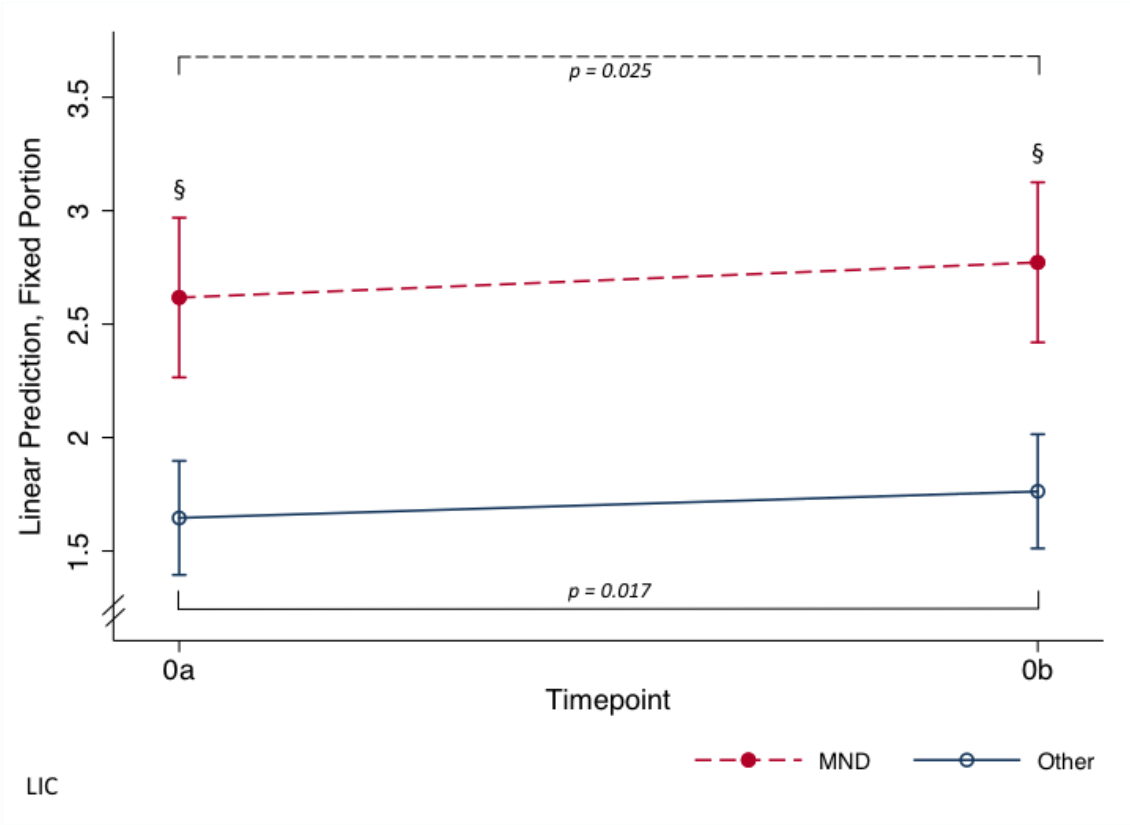

Figure 7-2: Linear mixed model – effect of time on LIC, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of time (pre and post a single-session of lung volume recruitment) on lung insufflation capacity (LIC, L), by disease type. ***Model significant and main effects of time and disease present***. *P*-values refer to statistically significant comparisons, where lines represent statistically significant differences within disease group over time (matching sub-group legend) and the "§" represents differences between disease type (MND vs Other NMDs) at Timepoint 0a and 0b (both $p<0.0001$).

		LIC (L)		VC (L)		LIC – VC (L)	
		Mean difference (95% CI)	***p*-value**	**Mean difference (95% CI)**	***p*-value**	**Mean difference (95% CI)**	***p*-value**
Between disease over time							
MND *vs.* Other	Time 0b – 0a	0.04 (-0.13, 0.21)	0.670	-0.04 (-0.12, 0.04)	0.359	0.07 (-0.10, 0.25)	0.406
Within disease over time							
Time 0b – 0a	MND	0.15 (-0.06, 0.36)	0.151	-0.05 (-0.15, 0.04)	0.250	0.21 (0.00, 0.41)	0.051
Time 0b – 0a	Other	0.12 (0.05, 0.18)	**0.0005**	-0.02(-0.05, 0.02)	0.377	0.13 (0.06, 0.21)	**0.001**

		C_{rs} (L/cmH_2O)		Specific C_{rs} (L/cmH_2O/L)	
		Mean difference (95% CI)	***p*-value**	**Mean difference (95% CI)**	***p*-value**
Between disease over time					
MND *vs.* Other	Time 0b – 0a	0.0038 (0.0030, 0.0187)	**0.008**	-0.0018 (-0.0088, 0.0052)	0.607
Within disease over time					
Time 0b – 0a	MND	0.0115 (0.0014, 0.0216)	**0.029**	0.0027 (-0.0002, 0.0055)	0.065
Time 0b – 0a	Other	0.0006 (-0.0025, 0.0038)	0.688	0.0045 (0.0007, 0.0082)	**0.021**

		PCF (L/min)		PCF_{LIC} (L/min)		PCF_{LIC} – PCF (L/min)	
		Mean difference (95% CI)	***p*-value**	**Mean difference (95% CI)**	***p*-value**	**Mean difference (95% CI)**	***p*-value**
Between disease over time							
MND *vs.* Other	Time 0b – 0a	16.5 (-3.3, 36.3)	0.101	-7.4 (-24.1, 9.3)	0.380	-24.1 (-51.2, 3.0)	0.081
Within disease over time							
Time 0b – 0a	MND	5.4 (-6.4, 17.3)	0.351	6.7 (-6.1, 19.5)	0.293	1.2 (-14.3, 16.8)	0.870
Time 0b – 0a	Other	-11.1 (-23.9, 1.8)	0.090	14.1 (3.9, 24.3)	**0.008**	25.3 (7.5, 43.2)	**0.006**

		FRC (L)		TLC (L)		RV (L)	
		Mean difference (95% CI)	***p*-value**	**Mean difference (95% CI)**	***p*-value**	**Mean difference (95% CI)**	***p*-value**
Between disease over time							
MND *vs.* Other	Time 0b – 0a	-0.16 (-0.31, -0.02)	**0.027**	-0.19 (-0.33, -0.05)	**0.007**	-0.16 (-0.29, -0.02)	**0.027**
Within disease over time							
Time 0b – 0a	MND	-0.16 (-0.32, 0.01)	0.057	-0.19 (-0.37, 0.00)	**0.049**	-0.14 (-0.33, 0.06)	0.154
Time 0b – 0a	Other	0.01 (-0.06, 0.07)	0.824	0.01 (-0.05, 0.07)	0.763	0.02 (-0.03, 0.07)	0.469

Table 7-5: Summary of the post-hoc comparisons of the immediate effects of a single-session of LVR on respiratory variables, by disease type.

Time = Timepoint; MND = motor neurone disease group, Other = Other neuromuscular disease group. *P*-values in **bold** indicate statistically significant values ($p<0.05$).

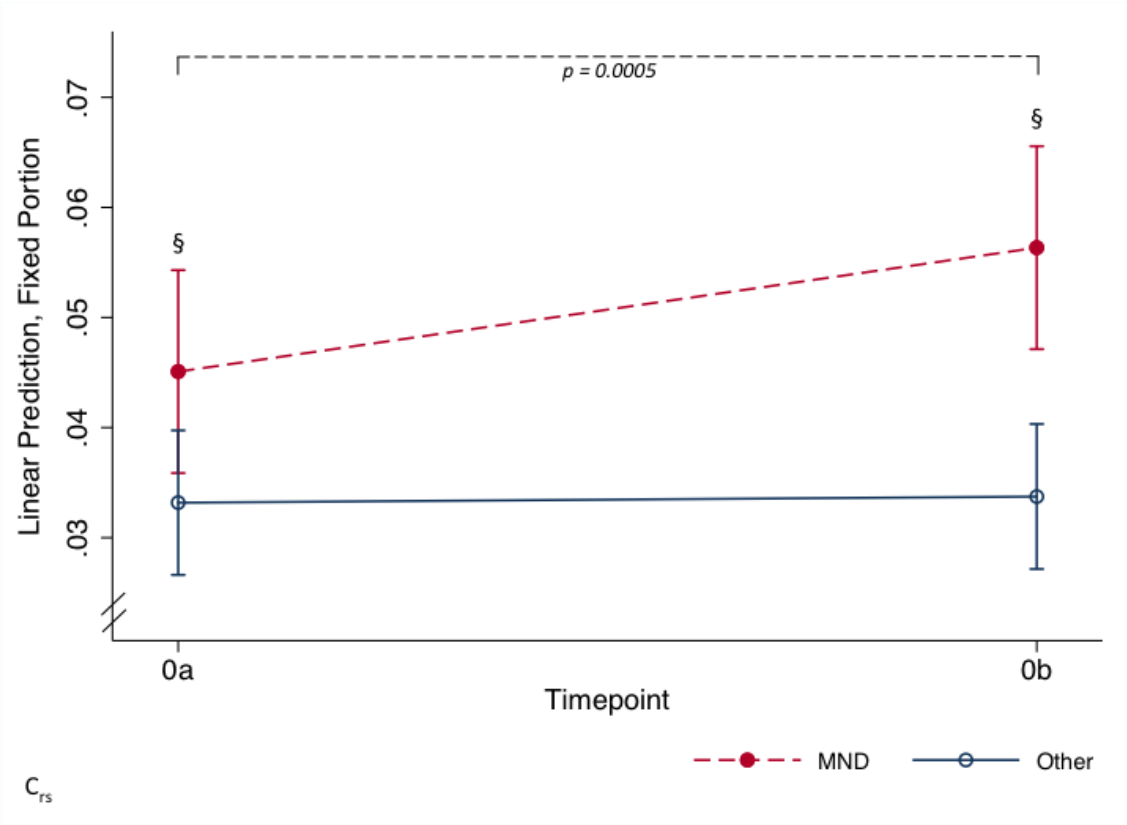

Figure 7-3: Linear mixed model – effect of time on C_{rs}, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of time (pre and post a single-session of lung volume recruitment) on respiratory system compliance (C_{rs}, L/cmH_2o) by disease type. ***Model significant and main effects of time, disease and an interaction effect present.*** *P*-values refer to statistically significant comparisons, where line represents statistically significant difference within disease group over time (matching sub-group legend) and the "§" represents differences between disease type (MND vs Other NMDs) at Timepoint 0a (p=0.04) and 0b (p<0.0001).

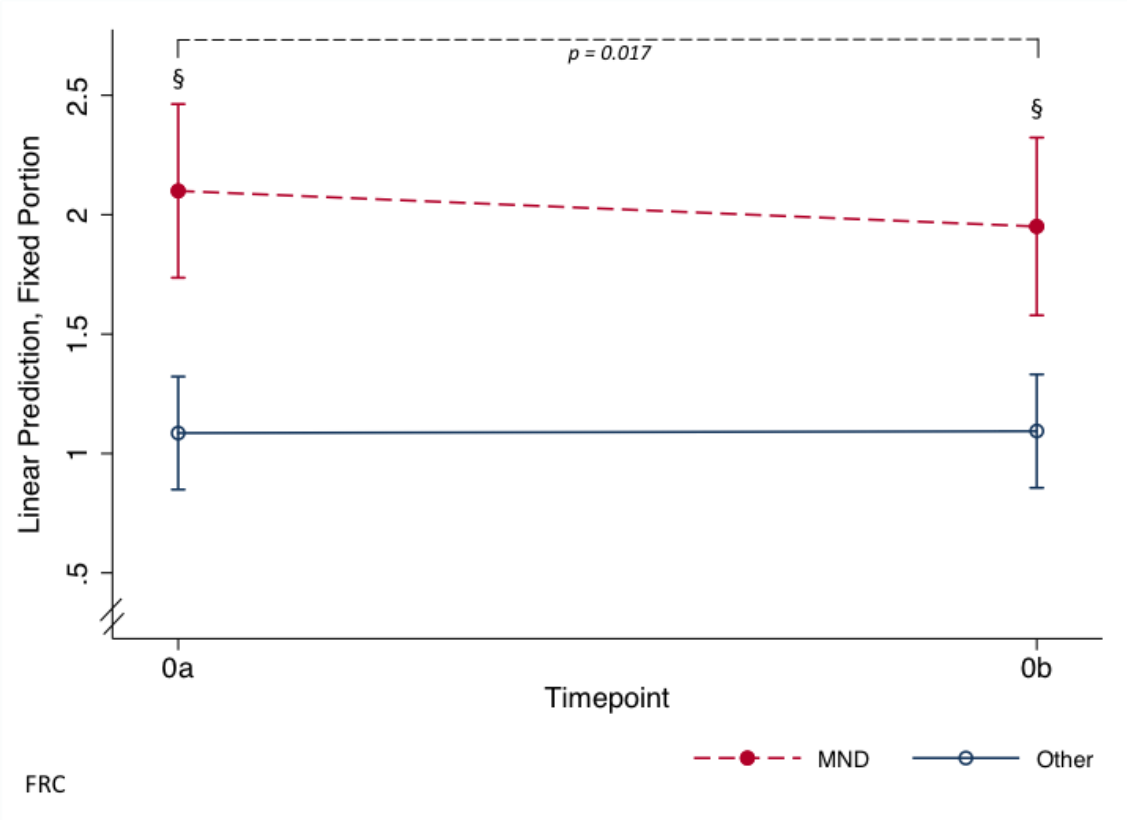

Figure 7-4: Linear mixed model – effect of time on FRC, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of time (pre and post a single-session of lung volume recruitment) on functional residual capacity (FRC, L), by disease type. ***Model significant and main effects of time, disease and an interaction effect present.*** *P*-values refer to statistically significant comparisons, where line represents statistically significant difference within disease group over time (matching sub-group legend) and the "§" represents differences between disease type (MND vs Other NMDs) at Timepoint 0a and 0b (both $p<0.0001$).

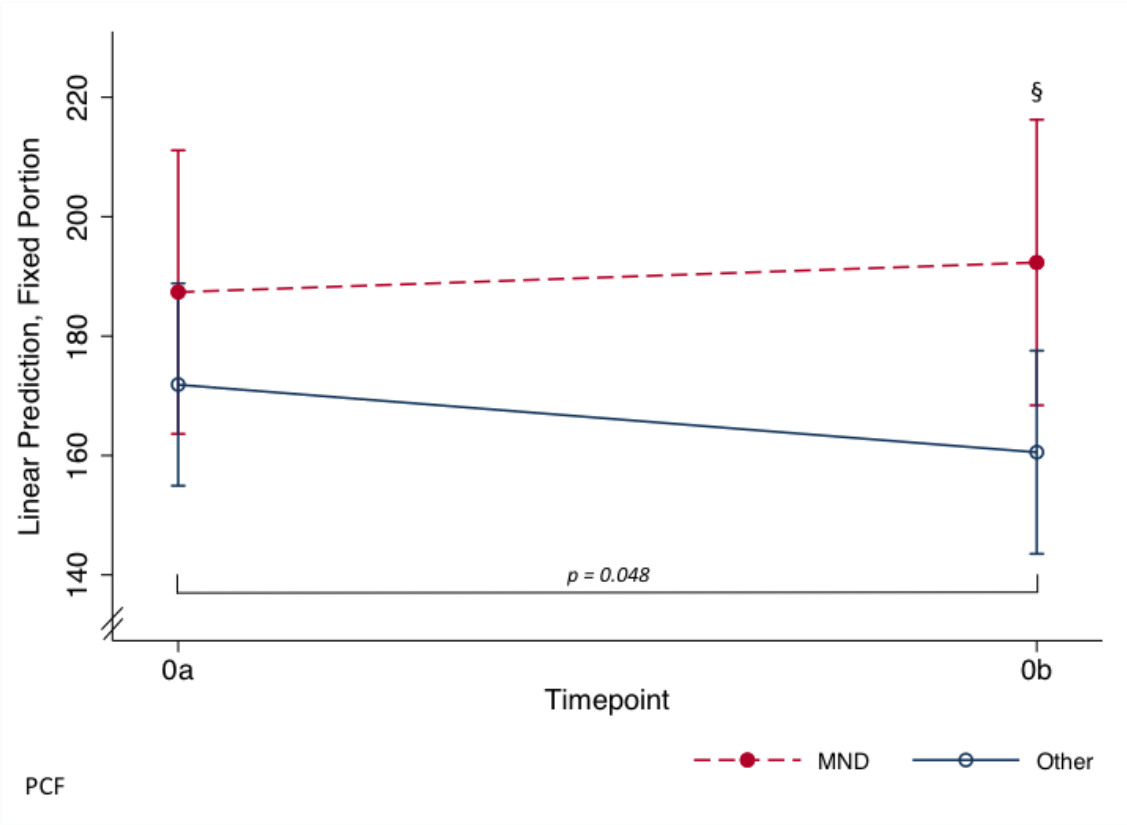

Figure 7-5: Linear mixed model – effect of time on PCF, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of time (pre and post a single-session of lung volume recruitment) on peak cough flow (PCF, L/min), by disease type. ***Model not significant and no main effects or interaction.*** *P*-values refer to statistically significant comparisons, where line represents statistically significant difference within disease group over time (matching sub-group legend) and the "§" represents difference between disease type (MND vs Other NMDs) at Timepoint 0b (p=0.034).

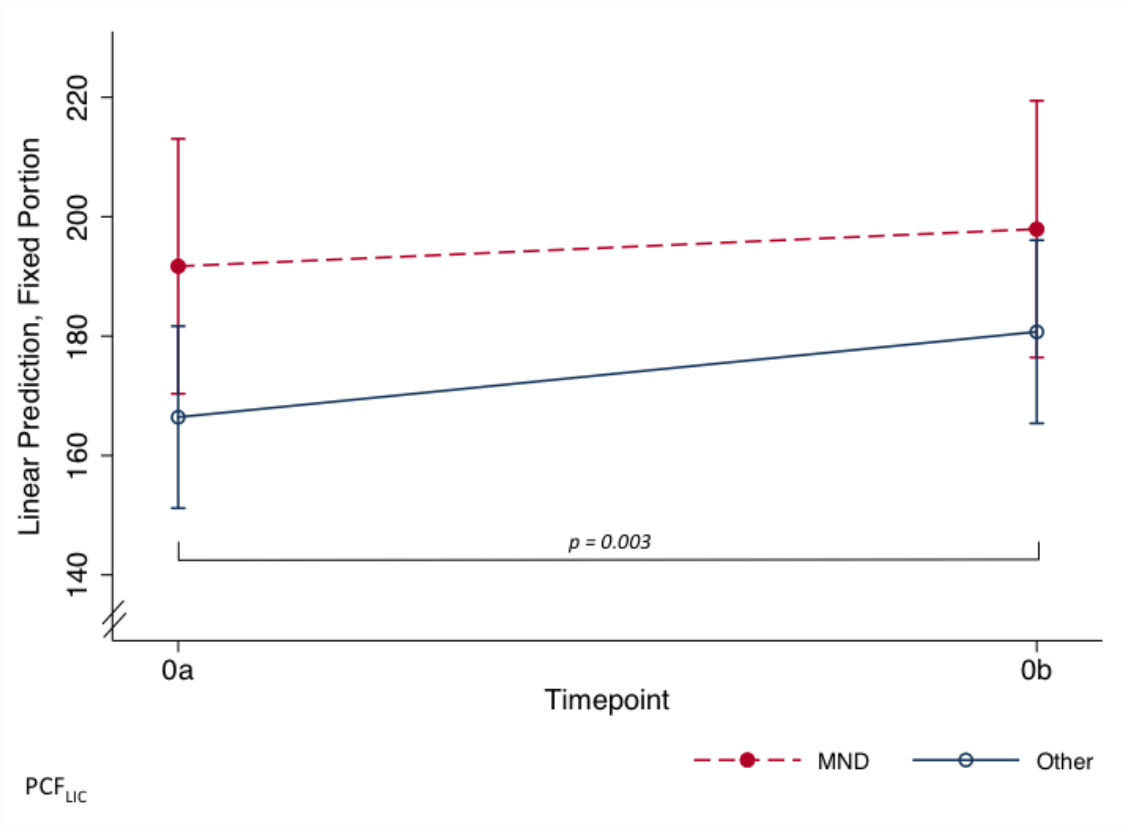

Figure 7-6: Linear mixed model – effect of time on PCF_{LIC}, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of time (pre and post a single-session of lung volume recruitment) on peak cough flow from lung insufflation capacity (PCF_{LIC}, L/min), by disease type. ***Model significant and main effect of time present***. *P*-values refer to statistically significant comparisons, where line represents statistically significant difference within disease group over time (matching sub-group legend).

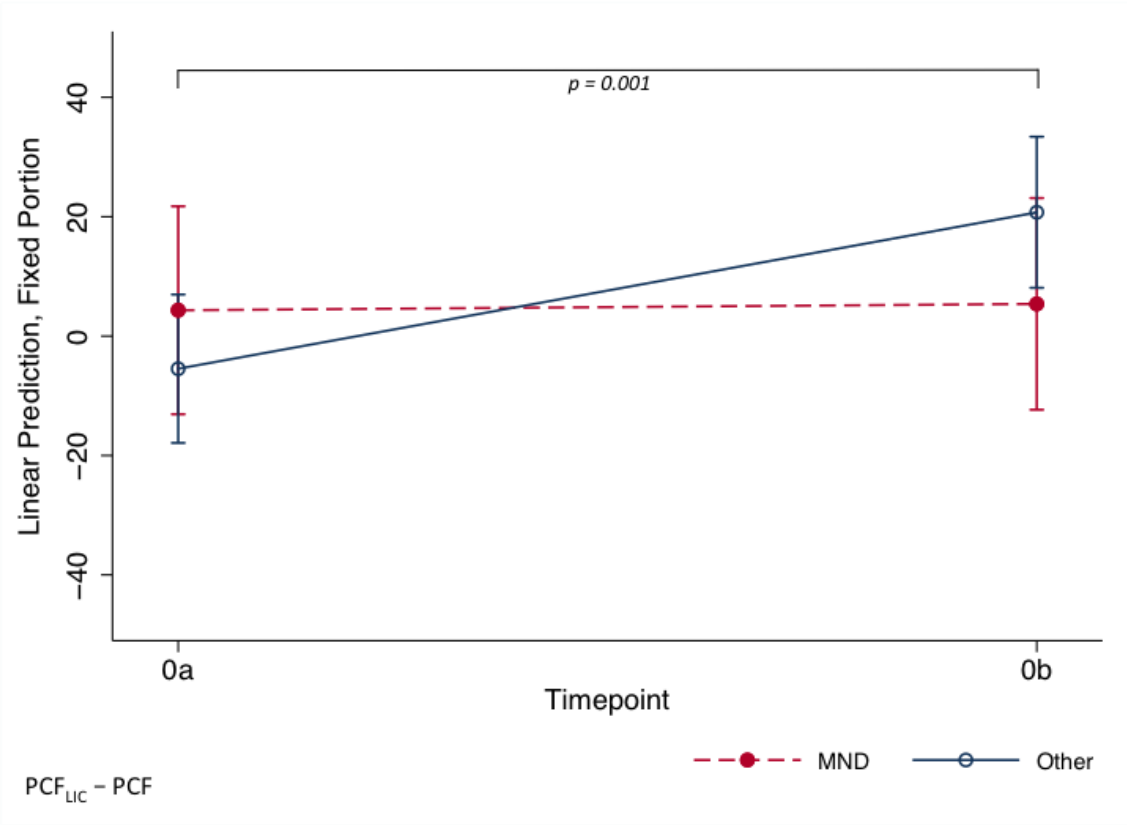

Figure 7-7: Linear mixed model – effect of time on the PCF_{LIC} – PCF difference, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of time (pre and post a single-session of lung volume recruitment) on the peak cough flow from lung insufflation capacity minus peak cough flow difference (PCF_{LIC} – PCF, L/min), by disease type. ***Model significant and main effect of time present.*** *P*-values refer to statistically significant comparisons, where line represents statistically significant difference within disease group over time (matching sub-group legend).

7.4.4 C_{RS} ANALYSIS

Acceptable C_{rs} scores were obtained from 81% of all participants (70% of participants with MND and 87% of people with Other NMDs). The linear model (p=0.0001) identified main effects of time, disease, and a disease by time interaction for C_{rs}. Post-hoc analysis suggested participants with MND had higher C_{rs} at both timepoints, and this increased after the single-session of LVR, whereas no change was observed in Other NMDs (Table 7-5). Specific C_{rs} on the other hand demonstrated a main effect of time, with modelling suggesting a statistically significant improvement in the Other NMD group more so than MND. No difference was found between disease-type once normalising for lung volume (FRC) to derive specific C_{rs} (Table 7-5).

To aid interpretation of these results, exploratory analysis was undertaken to ascertain the sub-set of participants with both C_{rs} and specific C_{rs} values. Of the 65 participants with C_{rs} measurements at Timepoints 0a and 0b (MND = 19), acceptable nitrogen washout measurements and hence specific C_{rs} scores were obtained for a total of 44 participants (MND = 10), meaning a third of participants with C_{rs} did not have paired FRC data to derive specific C_{rs}. Figure 7-8 illustrates that the two MND participants with the greatest C_{rs} improvement and the two Other NMD participants with the greatest C_{rs} decline were excluded from specific C_{rs} analysis. These data may explain why a statistical increase was observed in C_{rs} but not specific C_{rs} in MND, and there was no change in C_{rs} but an improvement in specific C_{rs} in Other NMDs.

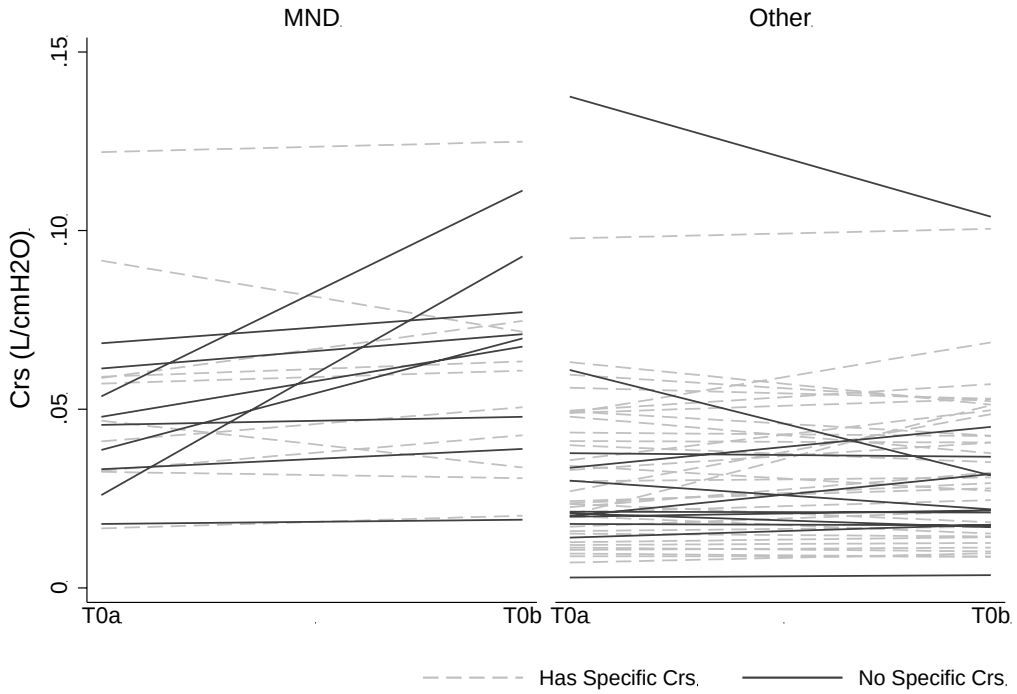

Figure 7-8: Respiratory system compliance before (T0a) and after (T0b) a single-session of LVR, for individual participants

MND = left panel; Other NMDs = right panel

Lines indicate participants with Specific C_{rs} measurements (dashed light grey) and those without Specific C_{rs} measurements (solid darker grey).

C_{rs} = respiratory system compliance measured in litres per centimetres of water, T0a = Timepoint 0a, T0b = Timepoint 0b, MND = motor neurone disease, Other = other neuromuscular disease.

Opposing directionality between C_{rs} and specific C_{rs} results may also be related to concomitant lung volume changes, due to the relationship between these three variables (Specific compliance = Compliance / Volume). The direction of change in C_{rs}, FRC and specific C_{rs} measurements are illustrated for participants with all three outcomes in Figure 7-9, with clinical interpretation considered in Table 7-6.

Four participants (MND = 1) demonstrated a fall in C_{rs}, FRC and Specific C_{rs}, whilst seven participants with Other NMD had a fall in C_{rs} and specific C_{rs} but an increase in FRC (quadrant C). Of the six participants in quadrant D, two had MND. The remaining 27 participants had changes in C_{rs}, FRC and specific C_{rs} over a single-session of LVR suggestive of benefit.

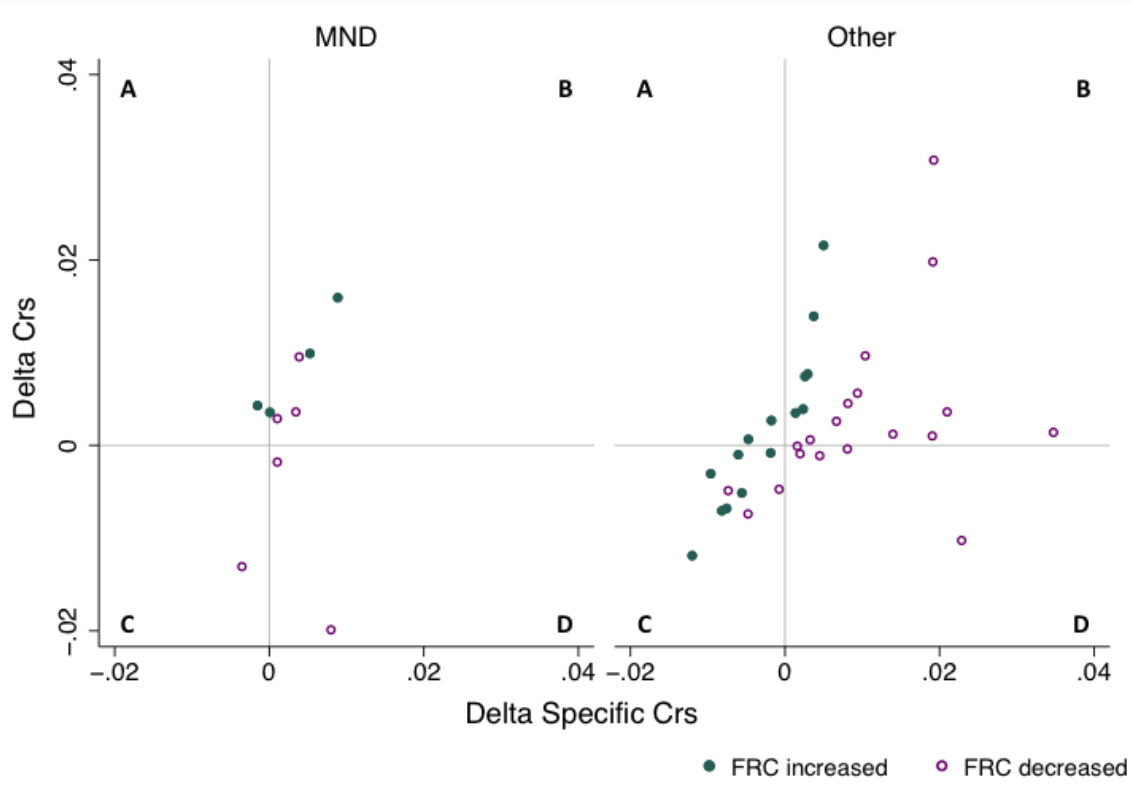

Figure 7-9: Change in respiratory system compliance (Delta C_{rs}, L/cmH_2O), specific respiratory system compliance (Delta Specific C_{rs}, L/cmH_2O/L) and functional residual capacity (FRC, L) over the course of a single-session of LVR, for individual participants.

Delta values represent Timepoint 0b minus 0a
Circles represent individual participants with all three outcome measures available (n=44). Letters refer to quadrant, with interpretation provided in Table 7-6.

Quadrant	Δ C_{rs}	Δ Specific C_{rs}	Δ FRC	Interpretation	Clinical Outcome
A	Increased	Decreased	Increased	C_{rs} and FRC both increased, however proportionally volume increased more than C_{rs}	Positive
B	Increased	Increased	Increased	C_{rs} and FRC both increased, however proportionally C_{rs} increased more than volume	Positive
B	Increased	Increased	Decreased	C_{rs} increased in context of a fall in lung volume	Positive
C	Decreased	Decreased	Increased	C_{rs} fell in the context of an increase in volume; the improvement in FRC being less than the loss of C_{rs}	Unclear
C	Decreased	Decreased	Decreased	Decline in both lung volume and C_{rs} observed	Negative
D	Decreased	Increased	Decreased	Decline in both lung volume and C_{rs} observed, however proportionally the loss of FRC was greater than the fall in C_{rs}. This suggests that underlying compliance remained unchanged	Unclear

Table 7-6: Interpretation of the interplay between the changes in respiratory system compliance, specific respiratory system compliance and functional residual capacity observed before and after a single-session of LVR

Letters (A, B, C, D) refer to the quadrants in Figure 7-9.
C_{rs} = respiratory system compliance, Specific C_{rs} = specific respiratory system compliance FRC = functional residual capacity

7.5 DISCUSSION

In this study of 80 participants with NMD, moderate to severe respiratory muscle weakness and lung volume restriction, over three quarters of the cohort (76%) could perform LVR successfully during their first attempt. After one-on-one training with a respiratory physiotherapist, all but four participants were able to achieve a maximal tolerated LIC of at least 10% above their spontaneous unassisted VC. This represented 5% of our study cohort, precluding meaningful comparison with the remaining 95% of participants to investigate demographic or respiratory function characteristics associated with LVR success or failure. Absolute LIC was higher in people with MND compared to other NMDs, however this latter sub-group were stiffer and more severely restricted with a lower baseline VC. Both groups could recruit a similar volume, reflected by no statistically significant difference in the LIC – VC difference, in either absolute magnitude (L) or relative to lung volume (%VC).

This data provides useful information regarding the number of people with NMD who can and can't successfully perform LVR, corroborating prior research. A case series of 108 patients with heterogeneous NMD including MND who presented for routine evaluation at a specialist neuromuscular clinic reported that 90 could achieve a MIC > VC, using a manual resuscitation bag or volume-limited ventilator. Of the remaining 16.7% patients, severe bulbar muscle dysfunction was cited as preventing LVR.[170] Another case series restricted to males with DMD reported that 74 of 78 consecutive patients (95%) could achieve MIC > VC when initially introduced to the technique, with cognitive impairment limiting LVR in the four remaining patients.[216] In patients with MND, 24 out of 26 participants (92%) could achieve a MIC > VC using a manual resuscitation bag and oro-nasal mask. Bulbar dysfunction was present in 15 participants, two of whom could not maintain glottic closure to perform LVR successfully.[215]

The success rates reported above are very similar to our findings in a naïve cohort of participants with more severe respiratory impairment and ventilatory needs. Our

participants used a manual resuscitation bag with a one-way valve. This negates the need for glottic control and likely explains why participants with moderate to severe bulbar dysfunction attained LIC > VC, unlike the study by Kang and Bach.[170]

As a group, people with heterogeneous NMD had statistically significant increases in C_{rs}, specific C_{rs}, LIC, LIC – VC, PCF_{LIC} and PCF_{LIC} – PCF following a single-session of LVR. *A priori* analyses by disease type demonstrated that LIC increased in both sub-groups following the single-session of LVR. There was no effect on VC or PCF across time, however the LIC – VC difference was greater at Timepoint 0b.

Interaction effects were found for C_{rs}, TLC, FRC and RV, suggesting that the two sub-groups (MND and Other NMDs) were not only different at baseline, but also responded differently the first time participants received LVR. People with MND demonstrated an improvement in C_{rs} and small reductions in TLC, FRC and RV, whilst no change was observed in Other NMDs. Paired, acceptable C_{rs} measurements demonstrated a mean improvement of 0.0038 (0.0001, 0.0075) L/cmH_2O (Table 7-3), primarily attributable to an improvement in participants with MND (0.0115 (0.0014, 0.0216) L/cmH_2O) (Table 7-5). In contrast, specific C_{rs} increased by a mean of 0.0041 (0.0011, 0.0070) L/cmH_2O/L (Table 7-3), with sub-group analysis demonstrating a statistically significant effect in the Other NMD group (0.0045 (0.0007, 0.0082) L/cmH_2O/L) but not MND. No between disease differences were noted (Table 7-5). These seemingly conflicting results may be a function of different sample sizes and therefore variance, between those with C_{rs} values (n=65) and the sub-set with specific C_{rs} (n=44). Almost a third of participants with paired C_{rs} measurements (Timepoint 0b and 0a) had no corresponding static lung volume trials, limiting the specific C_{rs} analysis.

Data from the 44 participants who did have C_{rs}, FRC and specific C_{rs} measurements does however allow us to speculate on the mechanisms behind the observed improvements. Figure 7-9 illustrates that following a single-session of LVR, over 60% of these participants had a numerical increase in compliance, which even if related to an increase in lung volume, represents a beneficial outcome (Table 7-6). Whilst these findings help unpack the efficacy of LVR, to fully understand the mechanism of effect invasive measurements of lung and chest wall compliance (C_L, C_{CW}) would be required

in addition to lung volumes – a technically challenging proposition in such a patient population.

Lechtzin and colleagues have conducted measurements of C_L but not C_{CW} pre and post a hyperinflation technique in people with MND, namely 5-minutes of single-breath inflations delivered by a non-invasive positive pressure mouthpiece ventilator (mean inspiratory pressure = 23 cmH_2O (range 19-30 cmH_2O). They found no overall change in C_L (mean change = 6.8 ± 23.2 mL/cmH_2O), however 5 out of 14 participants with MND did demonstrate an improvement >10% of baseline C_L.[159] Lechtzin *et al* postulated that resolution of atelectasis may be the mechanism by which C_L improved in those who responded to hyperinflation therapy. Our finding that 15 of 19 participants with MND had an immediate increase in C_{rs} value following LVR suggests a physiological mechanism that is quickly amenable to therapy such as alveolar recruitment, however it also introduces the possibility of an effect via a shift in lung volume, C_{CW} or attributable to measurement repeatability.

Although C_{rs} cannot differentiate between C_L and C_{CW}, its non-invasive methodology is an advantage as it can be performed in people with severe respiratory and physical impairment. The findings of an improvement in C_{rs} with no change in VC are similar to those of a smaller trial comparing the immediate effects of LVR in twelve people with NMD to twelve sex-matched healthy control participants.[78] Molgat-Seon and colleagues reported a 39.5 ± 9.8% increase in C_{rs} relative to baseline (increase in group mean from 37 ± 5 to 50 ± 7 mL/cmH_2O), with no change in VC, TLC, other compartmental lung volumes or PCF.[78] The improvement in C_{rs} herein (~8%) did not approach this magnitude, and may reflect our larger study population. We observed greater variation in our sample of 72 participants with C_{rs} measurements at baseline (group mean = 38 ± 25 mL/cmH_2O). Furthermore, the Other NMD sub-group who had comparable diagnoses to the twelve participants studied by Molgat-Seon and colleagues were stiffer (33 ± 25 mL/cmH_2O, n=49) and thus may not be as immediately responsive to a single-session of LVR. Our cohort was naïve to the technique, and we did not include a six second breath-hold at LIC.[78] It remains to be shown whether prior familiarity, practice or variation in technique (such as variable rates of compressions or

inclusion of a prolonged breath-hold at LIC) alter any effects. Additionally, it should be noted that this cohort excluded people who were unwell with acute respiratory issues, hence these findings can not be extrapolated to people with a concurrent RTI or pneumonia.

An improvement in C_{rs} could be hypothesised to translate to improved lung volume or cough effectiveness, however, despite the improvement in C_{rs} in people with MND reported above, this present study found no change in VC or PCF in either disease group. This is in agreement with the finding by Molgat-Seon and colleagues, who reported mean ± SEM pre- and post-LVR values for VC of 1.17 ± 0.23 *vs.* 1.21 ± 0.23 L, and PCF values of 149 ± 23 *vs.* 142 ± 19 L/min.[78] They also conducted inert gas dilution measurement of static lung volumes and found no significant improvement in the twelve participants with slowly-progressive NMDs. Our finding of no change in static lung volumes in the 38 people with Other NMDs corroborates this. Although we did find a statistically significant small drop in TLC, FRC and RV in people with MND, only eleven out of 27 participants with MND could perform paired measurements, hence these lung volume effects should be interpreted with caution.

In contrast to our findings and those of Molgat-Seon and colleagues, the only other published study to examine the short-term effect of LVR therapy (five maximal inflation breaths) did report an improvement in FVC and PCF.[219] An interaction effect was observed in a sample of 15 out of 29 participants with MND who had pre- and post-session FVC data in a cross-over intervention-control study. Mean FVC was higher after the LVR-session compared to after the Control period (2.30 ± 0.92 L *vs.* 2.11 ± 0.83 L, p=0.03), however there was no change over time in either the LVR or control arms (LVR pre = 2.23 ± 0.93 *vs.* post 2.30 ± 0.92 L compared to Control pre = 2.11 ± 0.86 *vs.* post 2.11 ± 0.83 L). The authors employed inappropriate statistical analyses for the cross-over design and misinterpreted their findings, hence their conclusion of an improvement in FVC is questionable.

The authors did find an improvement in *unassisted* PCF, with main effects for time, interventions and a significant interaction. Peak cough flow increased over time with LVR (pre-LVR = 251 ± 119 *vs.* post-LVR = 305 ± 141 L/min), and was greater post-LVR

than post-Control (PCF post-Control = 255 ± 121 L/min). An improvement in compliance was postulated as a possible mechanism, however C_{rs} was not measured. The mean PCF improvement of 54 L/min in the LVR arm was considerably higher than that found in the current study's MND sub-group (mean difference = 5 L/min, Table 7-3).

Cleary and colleagues measured PCF using a peak flow meter and did not describe their testing procedure, whereas an oro-nasal mask and pneumotachometer were used in this study according to the methods detailed in Section 3.7.4 and Chapter 4. No guidelines exist for PCF testing hence method and equipment may explain some of the discrepancy observed between the work by Cleary *et al,* and that by our and other data.[78] Additionally, normal intra-individual variability for PCF has not been well-established. Only one study has reported on the intra-individual variability of a PCF manoeuvre, finding a mean coefficient of variation in 12 healthy participants over 15 cough manoeuvres of 13.8% (range 8.7% to 23.2%), using a pneumotachometer.[127] Within-participant change that differs by *less* than these values may therefore reflect measurement "noise"; further research to describe the smallest worthwhile effect is necessary, plus explore the clinical significance of this measure.

The lack of improvement in VC, lung volumes or unassisted PCF in the current study may indicate that the improvement in C_{rs} observed in the MND sub-group was not great enough and/or sustained to produce a flow-on effect. Previously, the immediate effects of LVR on C_{rs} have been shown to diminish within one-hour post-LVR.[78]. Additional factors such as fatigue or alteration in abdominal pressure (e.g., after lunch) may also have countered the benefit.

Although the novel elements of this immediate effects study are the assessment of lung volumes, compliance and cough pre- and post- a therapy session in medically-stable people with NMD, the LIC and PCF_{LIC} data collected also adds to the body of literature regarding volume and cough augmentation. In keeping with prior work, in this study this method of assisted inflation increased LIC more than 10% above spontaneous unassisted VC in 95% of the cohort.[136,137,170,209,213,215,220,222] Furthermore, we found an improvement in LIC following the one-on-one session in both disease sub-

groups, with a group mean improvement of 130 mL (5, 210 mL). This increase may be attributable to a skill acquisition or learning effect considering our naïve population, or be associated with the improvement in C_{rs}.

Surprisingly and in contrast to previously published literature we found considerable variability in the "cough augmentation" effect (PCF_{LIC} – PCF difference), despite augmenting volume during the technique. In the sub-group of participants with Other NMDs, 53% (28 out of 53 people) achieved PCF_{LIC} greater than unassisted PCF at baseline, increasing to 72% after the LVR session (38 out of 53 participants). There was a significant improvement in PCF_{LIC} of 14 L/min over time (8% increase over baseline values), whereas unassisted PCF demonstrated a non-significant drop of 11 L/min (Appendix 11.4.1.1). Consequently, the PCF_{LIC} – PCF difference improved following the single-session in participants with Other NMD. In contrast, although the proportion of participants with MND who achieved a higher PCF_{LIC} than PCF at baseline was similar (15 of 27, 56%), this number did not change after the intervention session.

The variability in PCF_{LIC} – PCF difference in this study, meaning that LVR did not produce a clear cough augmentation benefit for all people with NMD, is likely explained by multiple factors. These include the severity of respiratory system involvement and associated fatigability of the group, their naïvety to LVR, and between-study variations in testing equipment and procedures.

Many previous studies showing a positive PCF_{LIC} – PCF difference (i.e., PCF_{LIC} > PCF) combined an assisted inflation with a MAC, which produces higher assisted PCF values than either element alone, if tolerated.[101,102,107,110,169-171,209,212,215,218,227] In the current study, we did not apply a MAC during the assisted PCF manoeuvre, as the first seven study participants did not tolerate this abdominal over-pressure.

The device used to measure PCF across various studies could also account for differences in results; many of the studies that did find a cough augmentation benefit using LVR used a peak flow meter to measure PCF and PCF_{LIC}.[101,102,169-171,209,212,218,227] It is well established that absolute error exists between values obtained using a peak flow meter compared to pneumotachometer, tested either with a waveform

generator, [113,117,120,292,293] biological controls[108,115,120,294] or patient populations.[108,116,294] Magnitude of disagreement depends on the precise brand used,[113,115,117,120,292-294] and can vary across low to high flow rates[108,120,292] and at higher harmonic-frequency content of the airflow.[117,292] This variable bias in particular is problematic, as it may result in a peak flow meter over-reading or under-reading true PCF within the same person, depending on the flow rate or airflow waveform frequency changes with different cough augmentation techniques. In the current study, PCF and PCF_{LIC} testing were standardised and used the gold-standard pneumotachometer, thereby minimising measurement error.

7.6 CONCLUSION

Lung insufflation capacity, PCF_{LIC}, the LIC – VC and PCF_{LIC} – PCF differences all increased in this population of 80 participants with heterogeneous NMD naïve to LVR following a single-session of therapy. Respiratory system compliance also improved, primarily due to an increase in people with MND. No change was found in the group's compartmental lung volumes; the small but statistically significant reduction in lung volumes in participants with MND should be interpreted with caution given few participants could perform pre- and post-session multi-breath lung volume washout testing. We saw no change in VC or PCF following the LVR session, either in the group as a whole or within disease sub-groups.

Lung volume recruitment is an extremely viable method for augmenting volume; almost all of this group of medically-stable participants with NMD could obtain a LIC above their VC using this technique. Given our population was naïve and we saw no change in static lung volumes, a training effect could be partially responsible for the improvement in LIC observed over time. Such skill acquisition may also be associated with the improvement in PCF_{LIC}, although greater passive elastic recoil associated with obtaining a higher LIC may be another possible mechanism. This pre-post intervention study will be repeated at the conclusion of the three-month RCT, thereby providing additional data to inform our understanding of mechanisms underlying the immediate effects observed herein.

8 RCT: The effect of Regular LVR in People with NMD

8.1 Introduction

To date, there have been no prospective, controlled studies that have evaluated the physiological effect of regular LVR. We conducted a RCT of LVR compared to an active control arm in the cohort of participants with NMD presented in Chapters 6 and 7. The effect of these treatments on respiratory function, including whether regular therapy alters HRQoL, symptoms, or the immediate effects of a single-session of LVR, are reported below. Concordance with prescribed therapy and dose-response are also examined.

8.2 Null Hypotheses

1. That performing regular LVR for three months will not change respiratory function, specifically LIC, VC, C_{rs}, or static lung volumes.
2. That performing regular LVR for three months will not alter participant quality of life or symptoms.
3. That there is no association between the amount of regular therapy performed and the change in respiratory function or quality of life over a three-month period (i.e., no dose-response).
4. That there are no side effects or adverse events associated with performing regular LVR.
5. That performing regular LVR for three months will not decrease the number of respiratory-related hospital presentations.
6. That performing regular LVR for three months will not improve the immediate physiological response to a single-session of LVR.

8.3 METHODS

A three-month, parallel arm RCT was conducted, according to the research project outlined in Chapter 3.

Participants underwent baseline assessment and the immediate pre-post intervention study (Timepoint 0) as per Chapter 6 and Chapter 7. Participants who could perform LVR successfully during Timepoint 0a or 0b, defined as achieving a LIC at least 10% greater than VC ((LIC minus VC difference / VC) multiplied by 100) >10%), proceeded to treatment group randomisation, stratified by disease type (MND or Other NMD sub-groups). The Intervention arm (LVR) and the Active control group (Control) both entailed breathing exercises prescribed twice-daily for three-months, as detailed in Section 3.5.

Participants were reviewed in their homes one month (Timepoint 1) and two months (Timepoint 2) post-randomisation. Three months post-randomisation, participants underwent the final study visit (Timepoint 3). This comprised final assessment of respiratory function and HRQoL (Timepoint 3a) and a second pre-post intervention study (standardised session of LVR and respiratory function testing, Timepoint 3b).

Table 8-1 summarises the outcomes measured, which were defined in Section 3.6. Equipment, procedures and measurement methods were detailed in Chapters 4 and 5.

Statistical analysis was detailed in Chapter 3, with LIC selected as the primary outcome to evaluate the effect of regular LVR. A linear mixed model approach was used to examine the fixed effect of treatment group (LVR or Control), time and the interaction between treatment and time as fixed effects, and participant as a random effect. Secondary *a priori* analyses added disease type (MND or Other NMD) to this model, to examine the effect of disease on response. Linear mixed models were repeated for secondary outcomes (VC, LIC – VC, static lung volumes, C_{rs}, specific C_{rs}, PCF) and HRQoL outcomes.

Linear mixed models were also employed for the repeated pre-post intervention study, using primary (C_{rs}) or secondary outcomes (LIC, static lung volumes, VC, specific C_{rs}, PCF) as the response variable, disease type (MND/Other) and time (T3a/T3b) as fixed effects, and person as a random effect. A second model added RCT treatment group (LVR/Active Control) as a fixed effect, to determine if being prescribed LVR twice-daily for three-months versus the active control influenced the short-term effect.

	Timepoint 0a	Timepoint 0b	Timepoint 1	Timepoint 2	Timepoint 3a	Timepoint 3b
Time	Time 0, Ax (a)	Time 0, Ax (b)	1-month	2-month	3-month, Ax (a)	3-month, Ax (b)
Location	Austin Health		Participant's Home	Participant's Home	Austin Health	
Duration	5-6 hours		2-3 hours	2-3 hours	5-6 hours	
Measures						
Demographic information	✓				✓	
Respiratory information	✓				✓	
VC	✓	✓	✓	✓	✓	✓
PCF	✓	✓	✓	✓	✓	✓
FVC, FEV_1	✓				✓	
MIP, MEP, SNIP	✓				✓	
Static lung volumes	✓	✓	✓	✓	✓	✓
C_{rs}	✓	✓	✓	✓	✓	✓
LIC	✓	✓	✓	✓	✓	✓
PCF_{LIC}	✓	✓	✓	✓	✓	✓
SRI	✓				✓	
AQoL-8D	✓				✓	
ALSFRS-R	✓ if MND				✓ if MND	
Other		Randomised Training session	Treatment review	Treatment review		Treatment review Usual care session

Table 8-1: Schedule of data collection: RCT

Ax (a) = pre-session assessment, Ax (b) = post-session assessment, VC = vital capacity, PCF = peak cough flow, FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 second, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure, SNIP = sniff nasal inspiratory pressure, C_{rs} = respiratory system compliance, LIC = lung insufflation capacity, PCF_{LIC} = peak cough flow from lung insufflation capacity, SRI = Severe Respiratory Insufficiency questionnaire, AQoL-8D = Assessment of Quality of Life questionnaire, ALSFRS-R = Revised Amyotrophic Lateral Sclerosis Functional Rating Scale, MND = motor neurone disease.

8.4 GENERAL RESULTS

8.4.1 PARTICIPANTS

Eighty consecutive participants were recruited (34% diagnosed with MND, 66% with Other NMD) as detailed in Chapter 6. Four participants did not meet the randomisation criterion during the initial study visit (Timepoint 0a or 0b) (Chapter 7). Demographic and HRQoL data for the 76 participants who proceeded to the RCT are provided in Table 8-2. Baseline respiratory function data by treatment group is presented in Appendix 11.5.2, Table 11-15.

Three participants did not complete the AQoL-8D at Timepoint 0a; health-state utility for the remaining cohort ranged from 0.31 to 1.00 (mean index = 0.65). For participants with MND, the calculated mean ALSFRS-R Slope at time of study enrolment was 1.2 (0.8, 1.6) in the LVR group versus 1.0 (0.6, 1.3) units/month in the Control arm (p=0.415).

Variable		LVR	Control
Age (years)	All	59.3 (27.8 – 68.3)	56.8 (35.6 – 67.6)
	MND	64.6 (55.2 – 68.3)	64.7 (59.2 – 76.6)
	Other	47.5 (26.6 – 67.1)	44.6 (28.5 – 60.4)
Gender (M:F)	All	21 : 16	19 : 20
	MND	8 : 4	9 : 4
	Other	13 : 12	10 : 16
Height (cm)	All	166.1 ± 15.3	164.7 ± 14.8
	MND	173.0 ± 10.0	172.8 ± 9.1
	Other	162.8 ± 16.4	160.7 ± 15.6
BMI (kg/m^2)	All	24.7 ± 7.2	24.7 ± 7.5
	MND	27.8 ± 6.4	24.1 ± 4.4
	Other	23.3 ± 7.3	25.0 ± 8.7
Age at symptom onset (years)	All	28.0 (4.8 – 64.2)	21.7 (3.8 – 62.0)
	MND	63.2 (48.7 – 66.5)	62.8 (56.6 – 75.0)
	Other	9.6 (3.4 – 28.0)	7.8 (3.1 – 21.7)

Variable		LVR	Control
Time since symptom onset (years)	All	12.7 (2.0 – 24.6)	17.8 (2.2 – 37.0)
	MND	1.9 (1.5 – 2.7)	2.1 (1.1 – 2.5)
	Other	20.9 (12.7 – 34.2)	24.5 (17.8 – 49.4)
NIV user (Y:N)	All	29 : 8	31 : 8
	MND	10 : 2	9 : 4
	Other	19 : 6	22 : 4
Gastrostomy (Y:N:F)	All	12 : 24 : 1	8 : 31 : 0
	MND	9 : 2 : 1	7 : 6 : 0
	Other	3 : 22 : 0	1 : 25 : 0
AQoL-8D Health-state Utility Index	All	0.67 (0.17) 0.68 (0.55 – 0.80)	0.64 (0.17) 0.64 (0.50 – 0.76)
	MND	0.68 (0.12) 0.70 (0.56 – 0.80)	0.63 (0.17) 0.60 (0.50 – 0.76)
	Other	0.66 (0.19) 0.67 (0.54 – 0.80)	0.64 (0.17) 0.65 (0.47 – 0.77)
SRI Summary Scale	All	44.6 (7.7) 44.5 (40.2 – 49.1)	44.3 (9.2) 46.3 (39.6 – 50.2)
	MND	43.2 (4.6) 42.8 (39.7 – 46.2)	42.1 (12.1) 42.5 (39.6 – 49.2)
	Other	45.2 (8.9) 45.3 (40.5 – 50.9)	45.4 (7.4) 46.7 (40.9 – 50.2)
ALSFRS-R score	MND	21.3 ± 6.6	26.7 ± 7.1
ALSFRS-R bulbar sub-score	MND	8.2 ± 4.2	9.5 ± 2.8
ALSFRS-R bulbar sub-score ≤9 (Y:N)	MND	6 : 6	5 : 8

Table 8-2: Demographic data for the 76 randomised participants by intervention and disease type sub-groups

Data are presented as mean ± standard deviation, median (lower quartile – upper quartile) or frequency count. Total number of participants in LVR group = 37 (MND, LVR = 12; Other, LVR = 25) and Active Control group = 39 (MND, Control = 13; Other Control = 26).

LVR = lung volume recruitment group; Control = active control group; MND = motor neurone disease; Other = other neuromuscular diseases including chest wall disease. M = male; F = female; BMI = body mass index; NIV = non-invasive ventilation; Y=yes, N=no, F=failed gastrostomy procedures; AQoL-8D = Assessment of Quality of Life 8D, SRI = Severe Respiratory Insufficiency questionnaire; ALSFRS-R = Revised amyotrophic lateral sclerosis functional rating scale. Bulbar sub-score ≤9 indicates moderate bulbar symptoms as per Smith 2018.[287]

One participant with MND withdrew from the study without undergoing any physiological measurements at their scheduled 1-month visit, citing advancing disease, difficulty performing the allocated intervention and the burden of study involvement. Two further participants were unable to complete their final visit within three-weeks of the scheduled Timepoint 3a visit but did have outcome measures collected at Timepoint 2. One of these participants had MND with disease-related issues preventing attendance (self-reported deterioration in functional and mental-health state, other appointments and procedures), and social issues prevented the final visit for the third participant (Other NMD) (Figure 8-1). Mean study duration for the 37 participants in the LVR group was 88.5 (12.5) days (total of 3276 participant days), compared to 90.6 (4.1) days for the 39 Control group participants (3533 participant days; mean difference = -2.0 (-6.3, 2.2) days, *p*=0.335).

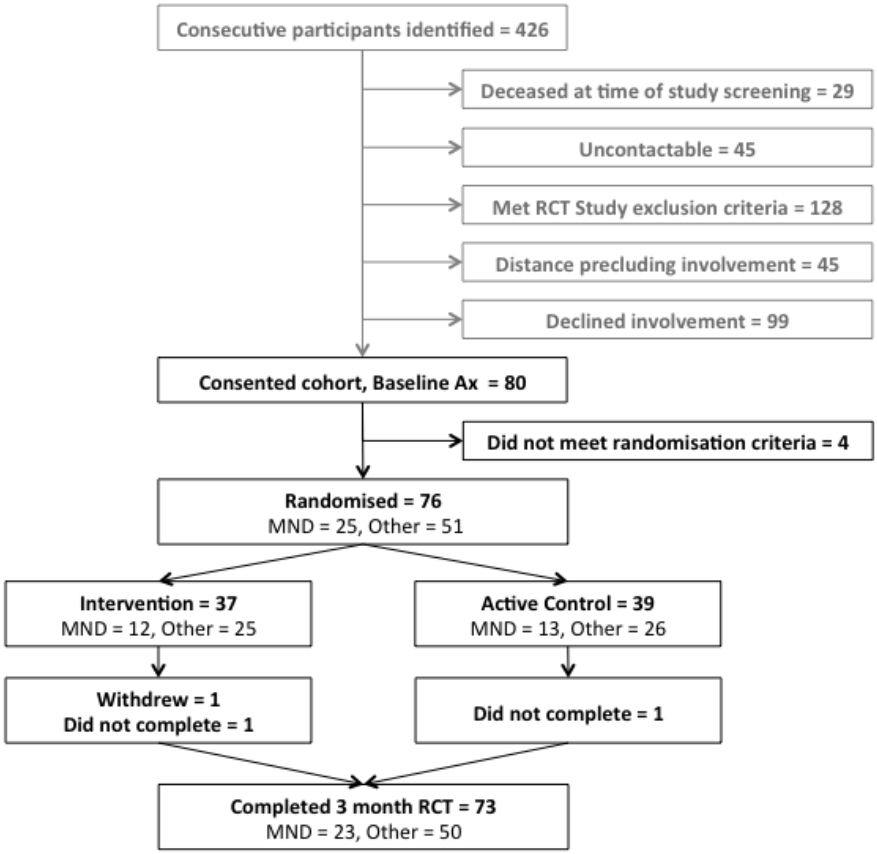

Figure 8-1: Study flow chart

Did not complete = participants unable to attend final visit (Timepoint 3) within 3 weeks of scheduled end date. MND = motor neurone disease, Other = other neuromuscular diseases including chest wall disease, Ax = assessment, RCT = randomised controlled trial.

8.4.2 THERAPY USAGE

Based on diary records, the LVR group reported performing significantly fewer therapy sessions per day than Control (1.2 (0.7) versus 1.5 (0.5) sessions/day; mean difference = -0.35 (-0.62, -0.07) sessions/day, p=0.015). Participants in the LVR group reported performing their intervention at least twice a day a median of 45% of the study duration, compared to 75% in the active Control group (p=0.060). No differences were identified between the treatment groups in the proportion of study days zero, one, or at least two therapy sessions were conducted (Figure 8-2, Figure 8-3, Table in Appendix 11.5).

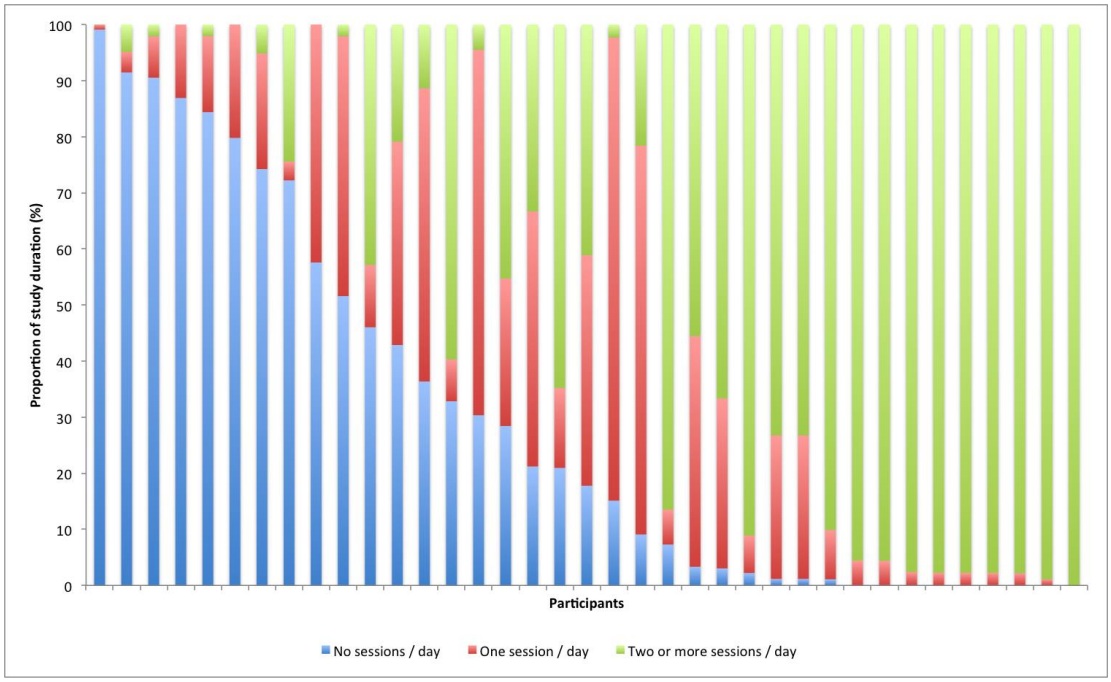

Figure 8-2: Self-reported LVR sessions per day, per participant

Proportion of study duration participants performed none, one or two or more LVR sessions a day, as reported in their diaries

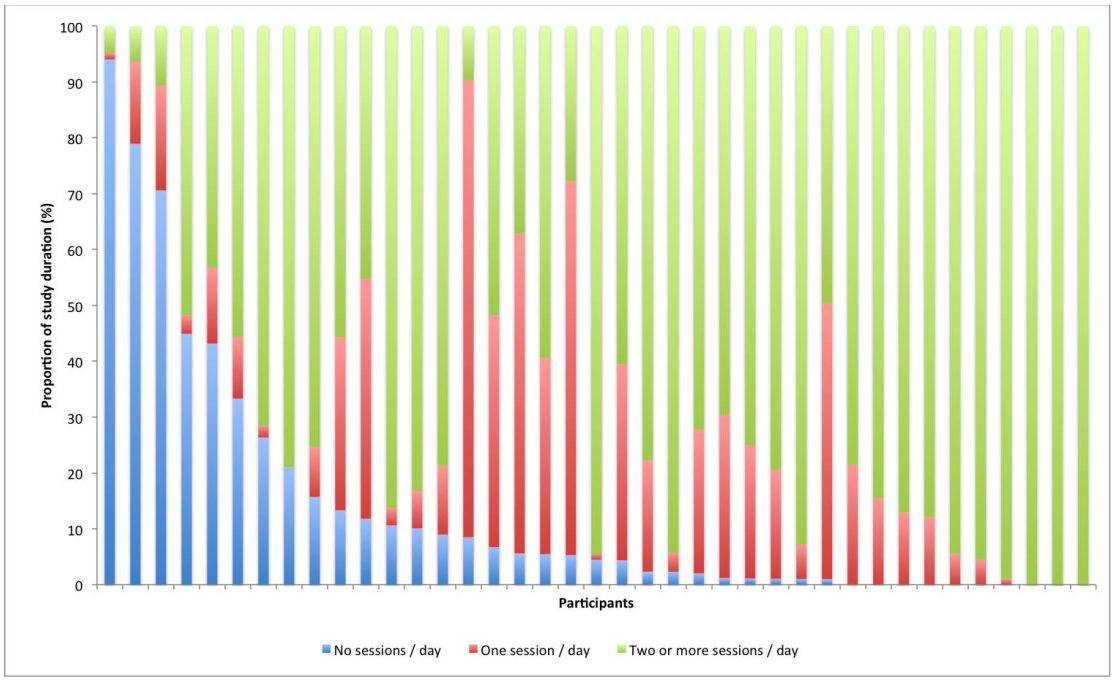

Figure 8-3: Self-reported Control sessions per day, per participant

Proportion of study duration participants performed none, one or two or more breathing exercise sessions a day, as reported in their diaries

There was substantial concordance overall between the average number of sessions per day recorded by the LVR counter and those reported by diary (Rho_{CCC} = 0.88 (95% CI = 0.80, 0.95), Pearson's r = 0.91, p<0.0001) (Figure 8-4). However, the LVR counter recorded fewer sessions than were diary-reported (average sessions/day = 1.00 ± 0.69, mean difference (95% limits of agreement) = -0.20 (-0.78, 0.38) sessions/day, p =0.0002; Figure 8-4).

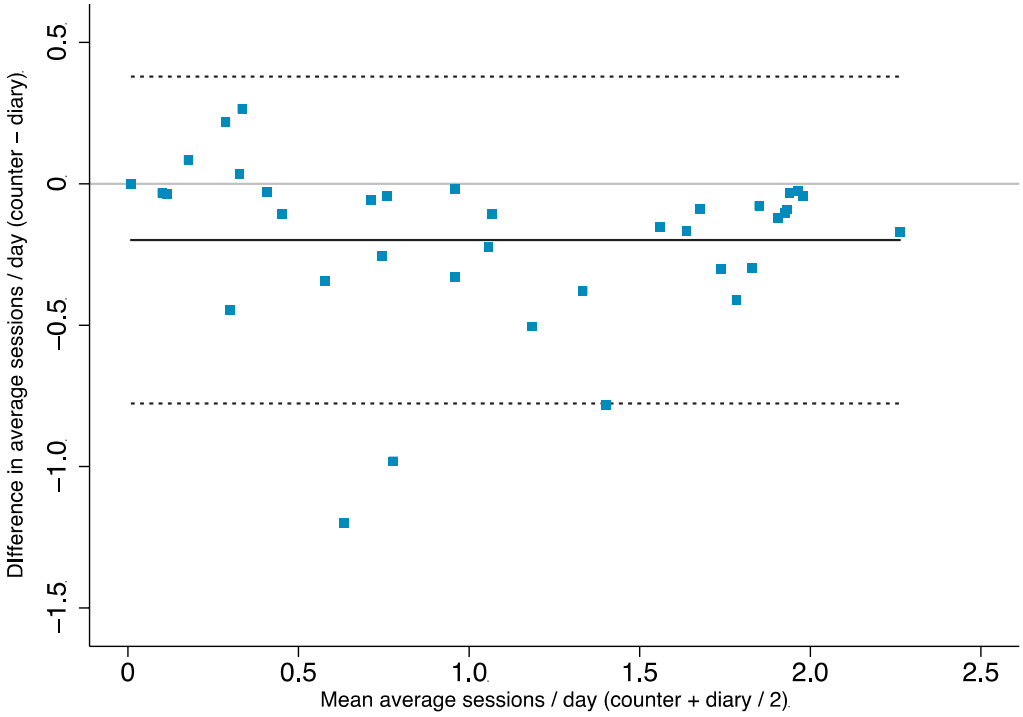

Figure 8-4: Bland and Altman plot measuring agreement between methods of evaluating LVR use

Plot illustrates the average number of LVR therapy sessions performed per day over the study duration, measured by LVR counter compared to diary self-report

LVR = lung volume recruitment. Light grey line (Y=0) represents the line of perfect average agreement. Solid dark grey line = observed average agreement, dashed dark grey lines = 95% limits of agreement.

Figure 8-5 illustrates the therapy usage based on the LVR counter (bottom panel) paired with that self-reported (top panel) for each participant. No clear cut-point was evident regarding percentage of days used versus not, on either self-report or LVR counter, suggesting that daily use could not be dichotomised into Yes or No. Hence, usage was considered a continuous variable and the average number of minutes per day of LVR therapy recorded by the LVR counter was used for analysis of dose-response.

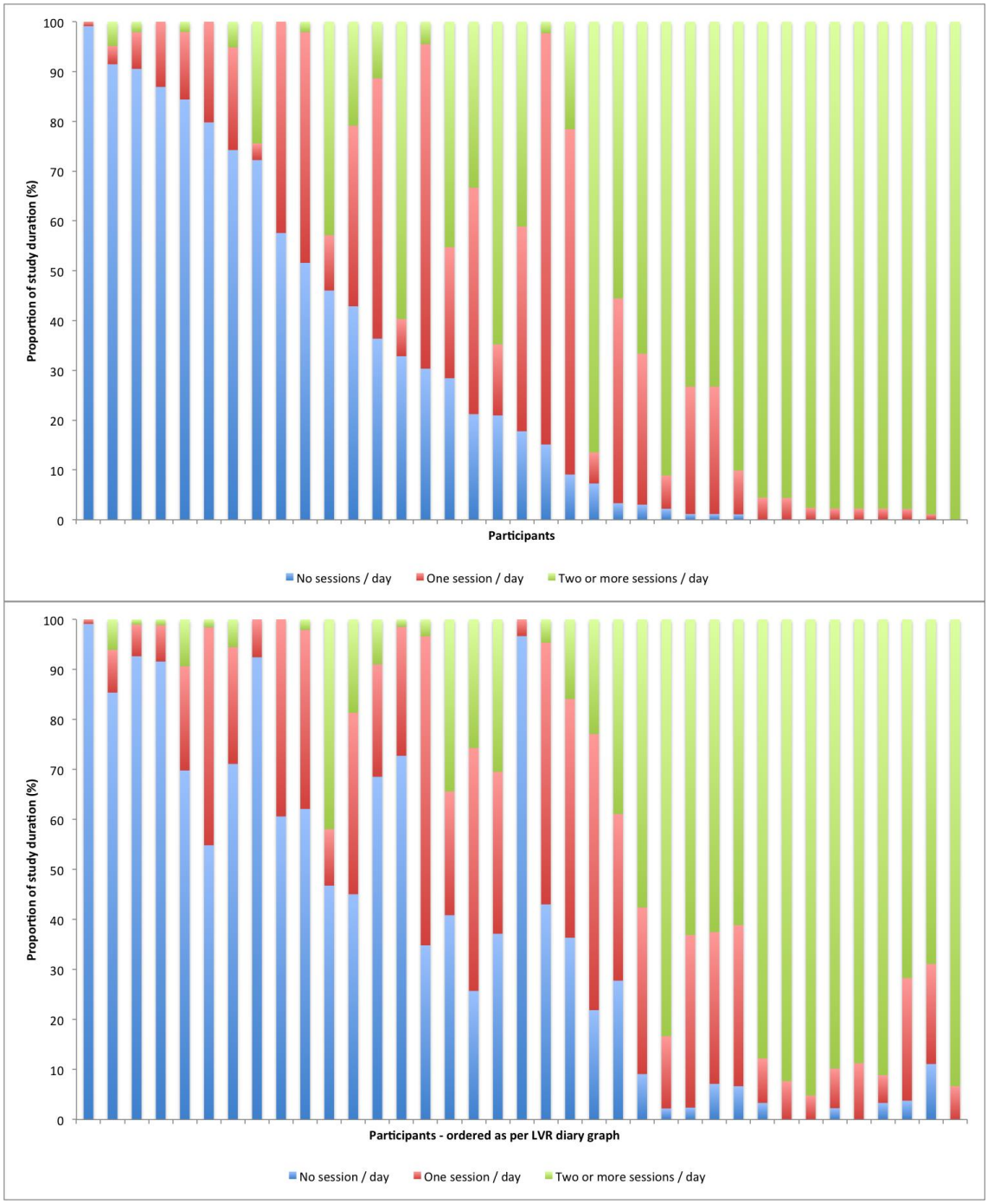

Figure 8-5: Recorded LVR sessions per day, per participant

Proportion of study duration participants performed none, one or two or more LVR sessions a day, as recorded by the LVR counter (bottom panel) compared to self-report (top panel). Participants are presented in the same order in both graphs.

8.5 RESULTS: PRIMARY HYPOTHESIS – LIC, VC AND C_{RS}

Findings of the linear mixed models, examining the effects of i) treatment and time, and ii) treatment, time and disease on respiratory variables, are presented in Table 8-3. The following sections explore these individual outcome measures further.

Variable model	df	χ^2	*p*-value
LIC model 1: log restricted likelihood = -179.8		***15.9***	***0.026***
Treatment	1	0.79	0.373
Time	3	0.21	0.975
Treatment*Time	3	14.91	**0.002**
LIC model 2: log restricted likelihood = -174.5		***44.4***	***0.0001***
Treatment	1	0.69	0.405
Time	3	0.08	0.994
Treatment*Time	3	18.47	**0.0004**
Disease	1	18.15	**<0.0001**
Treatment*Disease	1	0.16	0.689
Time*Disease	3	4.02	0.259
Treatment*Time*Disease	3	5.29	0.152
VC model 1 = -30.4		***16.0***	***0.025***
Treatment	1	0.29	0.593
Time	3	13.88	**0.003**
Treatment*Time	3	1.64	0.649
VC model 2 = -17.0		***73.8***	***<0.0001***
Treatment	1	0.06	0.812
Time	3	33.10	**<0.0001**
Treatment*Time	3	4.71	0.194
Disease	1	14.34	**0.0002**
Treatment*Disease	1	0.95	0.330
Time*Disease	3	33.64	**<0.0001**
Treatment*Time*Disease	3	5.74	0.125
LIC – VC model 1 = -103.7		***21.2***	***0.0034***
Treatment	1	0.90	0.343
Time	3	6.98	0.072
Treatment*Time	3	13.50	**0.004**

Variable model	df	χ^2	*p*-value
LIC – VC model 2 = -109.9		***28.2***	***0.020***
Treatment	1	1.49	0.223
Time	3	7.39	0.061
Treatment*Time	3	14.81	**0.002**
Disease	1	3.68	0.055
Treatment*Disease	1	0.67	0.413
Time*Disease	3	1.39	0.707
Treatment*Time*Disease	3	1.64	0.651
C_{rs} model 1 = 730.0		*8.4*	*0.300*
Treatment	1	8.17	0.681
Time	3	7.93	**0.048**
Treatment*Time	3	0.27	0.966
C_{rs} model 2 = 702.8		*22.7*	*0.090*
Treatment	1	0.19	0.662
Time	3	10.08	**0.018**
Treatment*Time	3	1.43	0.700
Disease	1	9.83	**0.002**
Treatment*Disease	1	0.09	0.762
Time*Disease	3	2.16	0.540
Treatment*Time*Disease	3	2.98	0.395
Specific C_{rs} model 1 = 526.0		***16.7***	***0.020***
Treatment	1	0.07	0.797
Time	3	11.95	**0.008**
Treatment*Time	3	5.41	0.144
Specific C_{rs} model 2 = 498.5		*22.1*	*0.105*
Treatment	1	0.13	0.715
Time	3	5.14	0.162
Treatment*Time	3	3.72	0.293
Disease	1	3.22	0.073
Treatment*Disease	1	0.16	0.693
Time*Disease	3	2.09	0.554
Treatment*Time*Disease	3	0.24	0.970

Table 8-3: Linear mixed models of effect of i) Treatment and Time, or ii) Treatment, Time and Disease on primary respiratory outcomes

Treatment represents Intervention (lung volume recruitment, LVR) or Control (active control breathing exercises); Time represents baseline (Time 0a) and final assessment (Time 3a);

Disease indicates motor neurone disease (MND) or other neuromuscular disease (Other); where Treatment, Time and Disease are fixed effects and participant a random effect. *P*-values in bold indicate statistically significant values ($p<0.05$).
LIC = lung insufflation capacity, VC = vital capacity, LIC – VC = LIC minus VC difference, C_{rs} = Total respiratory system compliance, Specific C_{rs} = C_{rs} divided by functional residual capacity

8.5.1 PRIMARY OUTCOME MEASURE: LUNG INSUFFLATION CAPACITY (LIC)

Linear models examining the effects of i) treatment and time, and ii) treatment, time and disease on LIC were statistically significant overall (Model 1 p=0.026, Model 2 p=0.0001, Table 8-3). A treatment by time interaction was found, whereby LIC increased in the LVR group over time. Lung insufflation capacity was higher at the one- and two-month study visits compared to baseline in the LVR intervention, whereas LIC fell in the active control arm one-month post-randomisation (Figure 8-6).

Post-hoc testing of the primary hypothesis (between-group comparison of change in LIC over three-months) revealed a non-statistically significant mean difference in observed data of 0.19 (0, 0.39) L (p=0.054). There was a statistically significant increase in LIC within the LVR group as a whole (p=0.039) (Table 8-4). Expressed as a percentage of baseline value, LIC increased by 12.2% (3.7, 20.7%) over the three-month treatment period in the LVR group, compared to 0.4% (-6.4, 7.3%) in the control arm (between-group comparison, p=0.031). Exploratory analysis of between-group change over time at one- and two-months suggested benefit in the LVR arm (mean difference Δ Time 1 – 0a = 0.33 (0.15, 0.51) L, p=0.0006; Δ Time 2 – 0a = 0.24 (0.05, 0.42) L, p=0.012).

When disease type was included in the model, a main effect of disease was also observed (Table 8-3): participants with MND had higher LIC values at all timepoints (Figure 8-7). Exploratory analysis suggested LIC increased with LVR within the first month and remained stable, and that this effect was predominantly attributable to the participants with Other NMD. Lung insufflation capacity was stable in the MND, LVR sub-group over time, whilst the decline in LIC observed in the MND, Control group on the linear model did not reach statistical significance on post-hoc testing (Table 8-4).

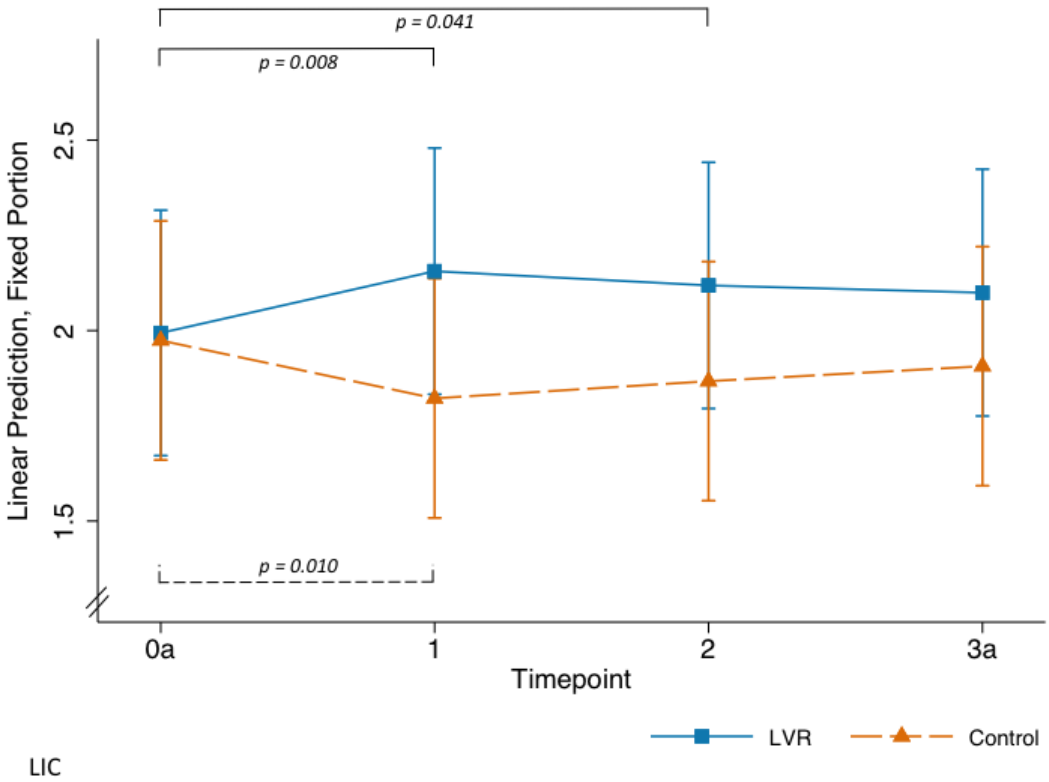

Figure 8-6: Linear mixed model – effects of treatment and time on LIC, for the whole cohort

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of treatment and time on lung insufflation capacity (LIC, L), for the whole cohort. ***Model significant and interaction effect between treatment and time present.*** *P*-values refer to statistically significant comparisons, where line patterns represent statistically significant differences over time by treatment group.

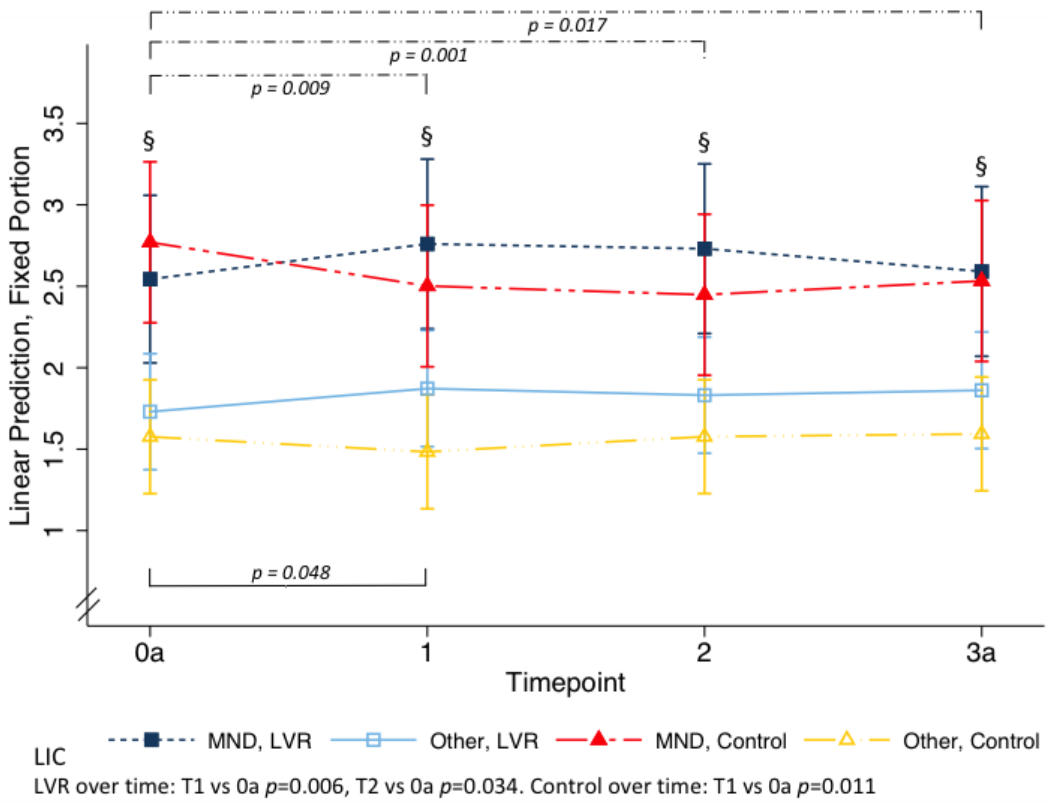

Figure 8-7: Linear mixed model – effects of treatment and time on LIC, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of treatment and time on lung insufflation capacity (LIC, L), by disease type**. *Model significant, main effect of disease and interaction effect between treatment and time present***. *P*-values refer to statistically significant comparisons, where line patterns represent statistically significant differences over time (matching sub-group legend i.e., "MND, Control" and "Other, LVR"), and "§" represents differences between disease type (MND vs Other NMDs, $p<0.0001$ at Timepoint 0a, 1, 2 and p=0.0002 for Timepoint 3).

LIC (L)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3a – 0a	33 : 39	0.19	0.00	0.39	0.054
Between-group at time						
LVR *vs.* Control	Time 0a	37 : 39	0.02	-0.46	0.50	0.934
LVR *vs.* Control	Time 3a	33 : 39	0.10	-0.35	0.56	0.652
Between disease type at time						
MND *vs.* Other	Time 0a	25 : 51	1.01	0.56	1.46	**<0.0001**
MND *vs.* Other	Time 3a	23 : 49	0.88	0.43	1.32	**0.0002**
Within-group over time						
Time 3a – 0a	LVR	33	0.13	0.01	0.25	**0.039**
Time 3a – 0a	MND, LVR	10	0.02	-0.34	0.38	0.889
Time 3a – 0a	Other, LVR	23	0.17	0.07	0.27	**0.002**
Time 3a – 0a	Control	39	-0.07	-0.22	0.09	0.380
Time 3a – 0a	MND, Control	13	-0.24	-0.64	0.16	0.221
Time 3a – 0a	Other, Control	26	0.02	-0.12	0.15	0.795
Time 3a – 0a	MND	23	-0.12	-0.38	0.13	0.331
Time 3a – 0a	Other	49	0.09	0.00	0.17	**0.041**

Table 8-4: Post-hoc comparisons of the observed effect of time and treatment on LIC

These data represent observed mean difference (95% confidence interval) in lung insufflation capacity (LIC, litres) across time and between groups. (n) = number of participants; Time = Timepoint; LVR = lung volume recruitment group; Control = active control group; MND = motor neurone disease group; Other = Other neuromuscular disease group. Shaded cells refer to comparisons that were statistically significant in the linear mixed models (Timepoints 0a and 3a only). **Bold** text refers to comparisons that were statistically significant on post-hoc testing of raw data.

8.5.2 VITAL CAPACITY (VC)

The model investigating the effect of treatment and time on VC was significant (p=0.025, Table 8-3). A main effect of time (p=0.003) was found, with VC falling over the course of the three-months. There was no significant treatment by time interaction; the decline was present in the LVR and Control groups, with no between-group difference present (p=0.645) (Table 8-5, Figure 8-8).

On adding disease type to the model (p<0.0001), a main effect of disease and a disease by time interaction were evident (Table 8-3). People with MND had higher VC compared to participants with Other NMDs, and declined over time regardless of treatment (MND mean difference Δ Time 3a – 0a = -0.25 (-0.36, -0.14) L, p=0.0001). Vital capacity remained stable in participants with Other NMDs, suggesting disease types responded differently over time, but the intervention did not modify that change (Table in Appendix 11.5.3, Figure 8-9).

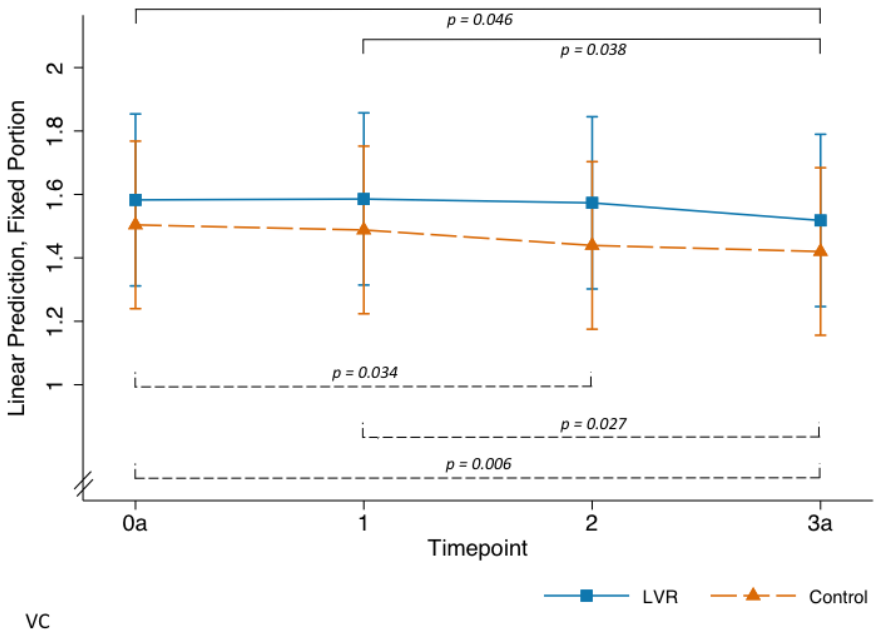

Figure 8-8: Linear mixed model – effects of treatment and time on VC, for the whole cohort

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of treatment and time on vital capacity (VC, L), for the whole cohort. ***Model significant and main effect of time present***. *P*-values refer to statistically significant comparisons, where line patterns represent statistically significant differences over time by treatment group.

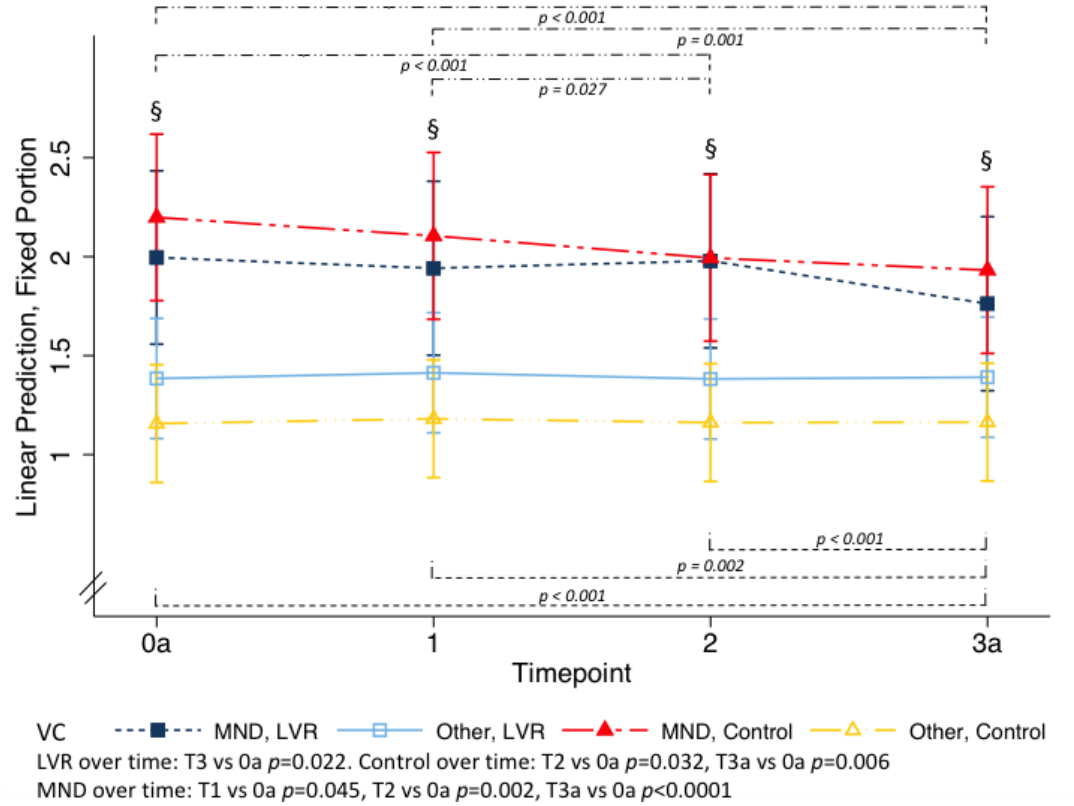

Figure 8-9: Linear mixed model – effects of treatment and time on VC, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of treatment and time on vital capacity (VC, L), by disease type. ***Model significant, main effects of time, disease and interaction effect between time and disease present.*** *P*-values refer to statistically significant comparisons, where § represents differences between disease type (MND vs Other NMDs, $p<0.0001$ for Times 0a, 1, $p=0.0002$ for Time 2 and $p=0.003$ for Time 3), and line patterns represent statistically significant differences over time (matching sub-group legend i.e., "MND, Control" and "MND, LVR").

8.5.3 LIC MINUS VC DIFFERENCE

The model investigating the effect on LIC – VC difference was statistically significant overall (Model 1 p=0.003, Table 8-3). A significant interaction between treatment and time was demonstrated; the LIC – VC difference increased in the LVR group over time (mean improvement 0.19 (0.09, 0.30) L, p=0.0008), whereas there was an initial decrease followed by return to baseline levels in the control group (Figure 8-10). A significant between-group difference was observed (mean difference 0.18 (0.00, 0.35) L, p =0.047) (Table 8-5).

The significant interaction between treatment and time remained when disease type was included in the model (Model 2 p=0.020, Table 8-3, Figure 8-11). No disease, treatment, or disease by treatment interaction effects were observed, suggesting that both disease types contributed to the improvement in LIC – VC. Analysis of the model suggested a statistically significant improvement over time in the MND, LVR sub-group (p=0.013) however this was not statistically significant in the Other, LVR sub-group (p=0.053). In contrast, post-hoc comparisons using the raw data demonstrated that the mean LIC – VC improvement of 0.17 (0.06, 0.28) L in the Other, LVR sub-group was statistically significant (p=0.004), whereas the increase of 0.25 (-0.04, 0.54) L in the MND, LVR sub-group was not (p=0.082) (Table in Appendix 11.5.3).

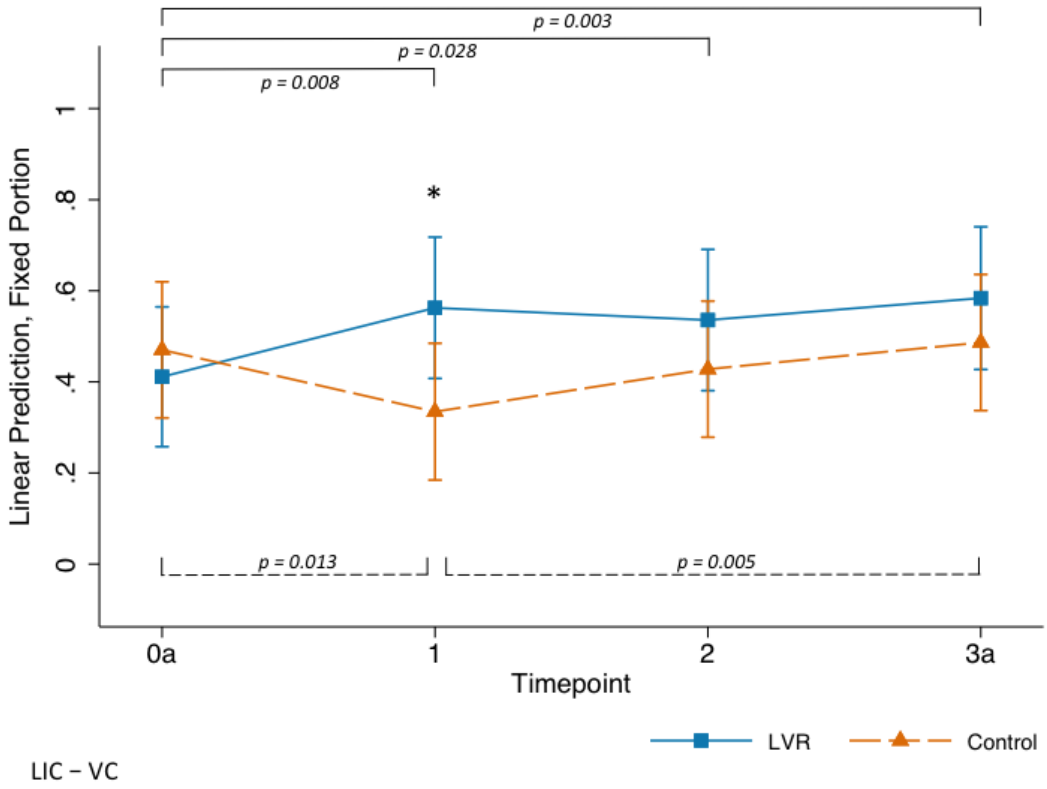

Figure 8-10: Linear mixed model – effects of treatment and time on LIC – VC, for the whole cohort

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of treatment and time on lung insufflation capacity minus vital capacity difference (LIC – VC, L), for the whole cohort. ***Model significant and interaction effect between treatment and time present.*** *P*-values refer to statistically significant comparisons between the estimated margins, where * represents differences between treatments (LVR vs Control) at Time 1 (*p*=0.038), and line patterns represent statistically significant differences over time by treatment group.

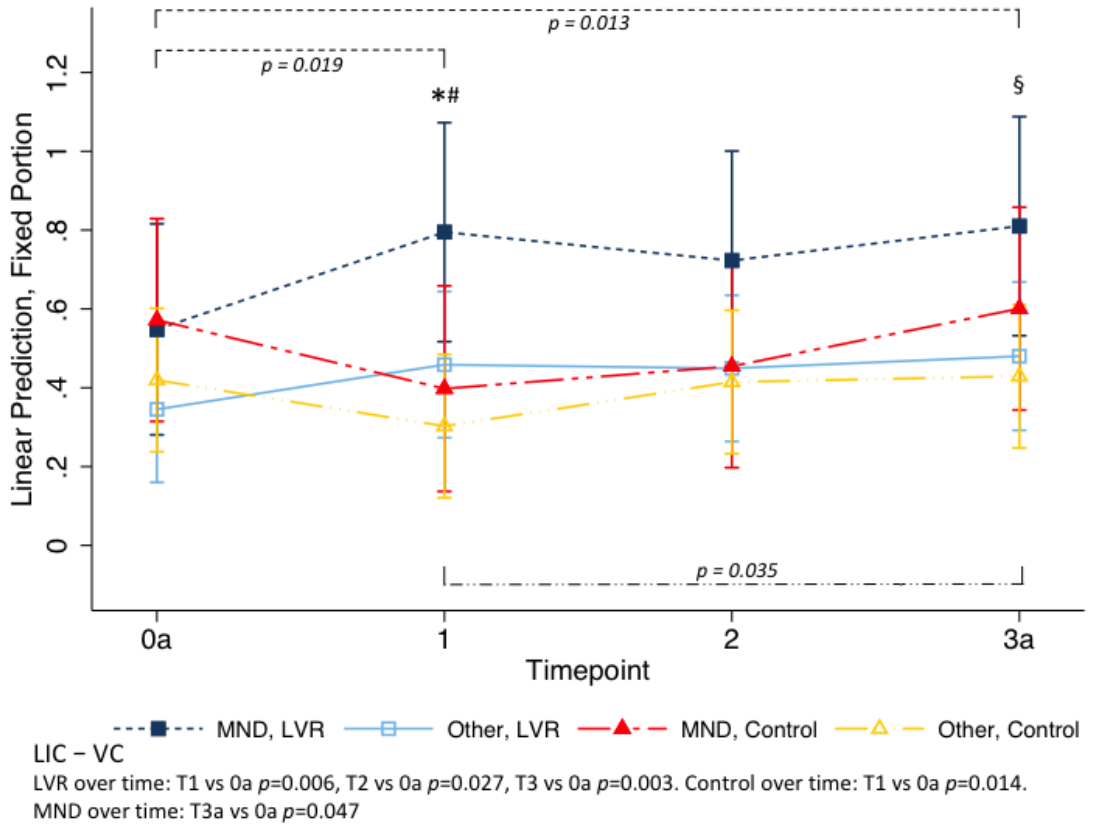

Figure 8-11: Linear mixed model – effects of treatment and time on LIC – VC, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of treatment and time on lung insufflation capacity minus vital capacity difference (LIC – VC, L), by disease type. ***Model significant and interaction effect between treatment and time present.*** *P*-values refer to statistically significant comparisons between the estimated margins, where * represents differences between treatments (LVR vs Control) at Time 1 (p=0.019), # represents differences between treatments by disease (MND, LVR vs MND, Control) at Time 1 (p=0.041), § represents differences between disease type (MND vs Other NMDs, p=0.033 for Time 3), and line patterns represent statistically significant differences over (matching sub-group legend i.e., "MND, Control" and "MND, LVR").

8.5.4 RESPIRATORY SYSTEM COMPLIANCE (C_{RS})

The two models examining the effects on C_{rs} were not significant overall. A main effect of time was found, with both the LVR and Control groups increasing over the study (Table 8-3). Post-hoc analysis suggested this improvement reached statistical significance within the LVR group but not within the Control arm (Table 8-5, Figure 8-12), however given the lack of overall model significance these findings should be interpreted with caution. There was no statistically significant difference between the treatment arms regarding the magnitude of change over three-months (mean difference 0.0015 (-0.0088, 0.0118) L/cmH_2O, *p*=0.773) (Table 8-5).

A main effect of disease was found when included in the model, with the MND group having higher C_{rs} values at all timepoints compared to the Other NMD group, regardless of treatment (Table in Appendix 11.5.3). Again, there were no interaction effects and the model overall was not statistically significant.

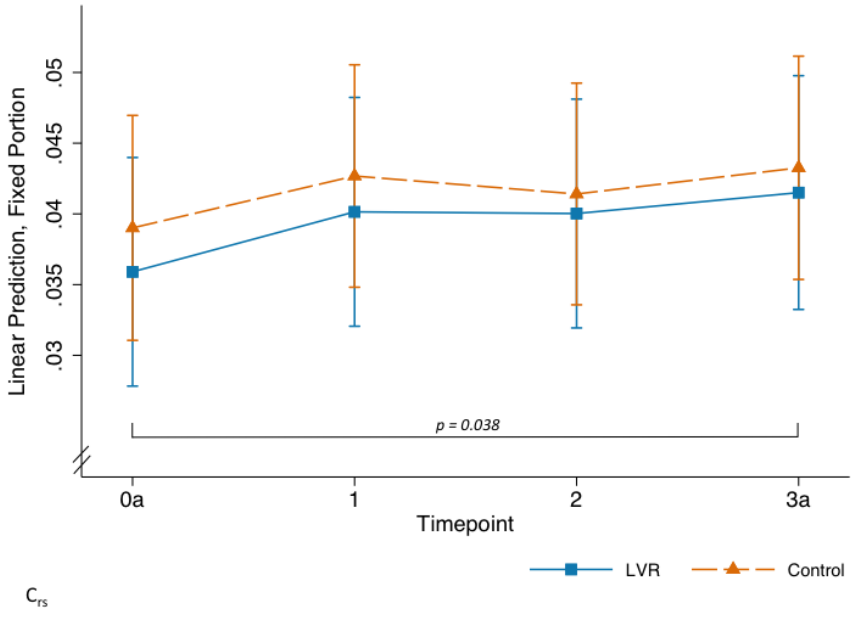

Figure 8-12: Linear mixed model – effects of treatment and time on C_{rs}, for the whole cohort

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of treatment and time on respiratory system compliance (C_{rs}, L/cmH_2O), for the whole cohort. ***Model not significant however main effect of time present.***

8.5.5 SPECIFIC RESPIRATORY SYSTEM COMPLIANCE (SPECIFIC C_{RS})

When expressing respiratory system compliance as a function of FRC to control for any change in lung volume, the model was significant overall (p=0.020) and a main effect of time was observed (p=0.008, Table 8-3). Post-hoc analysis demonstrated an improvement in specific C_{rs} in participants randomised to LVR between baseline and final study visit of 0.0160 (0.0032, 0.0287) L/cmH_2O/L (p=0.016), and no change in the Control group. However, no treatment effect or between-group differences were identified (Table 8-5, Figure in Appendix 11.5.4).

When disease was added as a factor, the model was no longer statistically significant (p=0.105) and there were no effects of time, treatment, disease or any interactions present (Table 8-3).

		LIC (L)		VC (L)		LIC – VC (L)	
		Mean difference (95% CI)	***p*-value**	**Mean difference (95% CI)**	***p*-value**	**Mean difference (95% CI)**	***p*-value**
Between group over time							
LVR *vs.* Control	Time 3a – 0a	0.19 (0.00, 0.39)	0.054	0.02 (-0.08, 0.12)	0.645	0.18 (0.00, 0.35)	**0.047**
Within group over time							
Time 3a – 0a	LVR	0.13 (0.01, 0.25)	**0.039**	-0.06 (-0.13, 0.01)	0.078	0.19 (0.09, 0.30)	**0.0008**
Time 3a – 0a	Control	-0.07 (-0.22, 0.09)	0.380	-0.08(-0.16, 0.00)	**0.038**	0.02 (-0.12, 0.15)	0.812

		C_{rs} (L/cmH_2O)		Specific C_{rs} (L/cmH_2O/L)	
		Mean difference (95% CI)	***p*-value**	**Mean difference (95% CI)**	***p*-value**
Between group over time					
LVR *vs.* Control	Time 3a – 0a	0.0015 (-0.0088, 0.0118)	0.773	0.0093 (-0.0053, 0.0238)	0.207
Within group over time					
Time 3a – 0a	LVR	0.0063 (0.0004, 0.0121)	**0.036**	0.0160 (0.0032, 0.0287)	**0.016**
Time 3a – 0a	Control	0.0048 (-0.0038, 0.0133)	0.267	0.0067 (-0.0013, 0.0148)	0.097

Table 8-5: Summary of the post-hoc comparisons of the observed effects of regular LVR on lung insufflation capacity, vital capacity and respiratory system compliance, by treatment group.

These data represent observed mean differences (95% confidence intervals) across time and between groups. Time = Timepoint, where Time 3a – 0a = final minus baseline values; LVR = lung volume recruitment group; Control = active control group. *P*-values in **bold** refer to comparisons that were statistically significant on post-hoc testing of raw data ($p<0.05$).

8.6 RESULTS: PRIMARY HYPOTHESIS – STATIC LUNG VOLUMES

There were no significant effects of time or treatment on FRC, when the group was considered as a whole. The model including disease was significant overall (p=0.0002), with a main effect of disease identified (p<0.0001) (Table 8-6). Participants with MND had higher absolute FRC at all timepoints compared to participants with Other NMDs, regardless of treatment group. Although post-hoc exploratory analysis suggested a small degree of variability in the Other, Control sub-group over time, there were no effects of treatment, time or disease, and no change in observed data over time (Table 8-7, Table in Appendix 11.5.3, Figure in Appendix 11.5.4).

The models for RV and TLC produced similar findings to FRC. The models examining the effects of time and treatment were not significant overall, and there were no significant main effects or interaction (Table 8-6). The models including disease as a variable were significant (RV p=0.0007, TLC p=0.0008). There were significant main effects of disease on RV and TLC (Table 8-6). Post-hoc analysis demonstrated that people with MND had higher RVs and TLCs at all timepoints compared to participants with Other NMDs. No effects of treatment, time or interaction between these variables were found (Table in Appendix 11.5.3).

No overall model effects or treatment effects were evident for ERV or IC (Table 8-6). Whilst a significant effect of time was found for ERV (p=0.008), there was no difference between the final and baseline assessments. Post-hoc exploratory comparisons suggested a statistically significant increase in the LVR group at Timepoint 1 that subsequently returned to baseline values, and no change in the Control arm (Figure in Appendix 11.5.4).

When disease was included as a factor, the models for ERV and IC were significant overall (ERV p=0.0002, IC p=0.0008, Table 8-6). As per other static lung volumes, the disease effect was attributable to higher ERV and IC values in people with MND (Table in Appendix 11.5.3, Figure in Appendix 11.5.4). Additionally, a main effect of time and a disease by time interaction were present for IC. Post-hoc analysis suggested that IC

declined over time (Timepoint 3a minus Timepoint 0a) in people with MND regardless of treatment (mean difference of -0.22 (-0.34, -0.10) L, *p*=0.002).

Variable model	df	χ^2	*p*-value
FRC model 1 = -158.4		*10.8*	*0.149*
Treatment	1	0.23	0.630
Time	3	7.14	0.067
Treatment*Time	3	2.77	0.429
FRC model 2 = -151.6		***41.8***	***0.0002***
Treatment	1	0.38	0.538
Time	3	5.78	0.123
Treatment*Time	3	2.38	0.498
Disease	1	24.9	**<0.0001**
Treatment*Disease	1	0.27	0.601
Time*Disease	3	1.39	0.707
Treatment*Time*Disease	3	3.23	0.358
RV model 1 = -127.6		*10.2*	*0.176*
Treatment	1	0.48	0.486
Time	3	5.51	0.138
Treatment*Time	3	3.51	0.319
RV model 2 = -122.6		***38.6***	***0.0007***
Treatment	1	0.33	0.568
Time	3	7.04	0.071
Treatment*Time	3	2.52	0.472
Disease	1	21.3	**<0.0001**
Treatment*Disease	1	0.02	0.897
Time*Disease	3	1.66	0.646
Treatment*Time*Disease	3	4.89	0.180
TLC model 1 = -175.5		*8.7*	*0.273*
Treatment	1	0.00	0.983
Time	3	6.37	0.095
Treatment*Time	3	2.19	0.535

Variable model	df	χ^2	*p*-value
TLC model 2 = -168.8		***38.2***	***0.0008***
Treatment	1	0.02	0.892
Time	3	6.45	0.092
Treatment*Time	3	1.41	0.703
Disease	1	23.54	**<0.0001**
Treatment*Disease	1	0.29	0.593
Time*Disease	3	1.36	0.716
Treatment*Time*Disease	3	3.46	0.326
ERV model 1 = 94.3		*14.1*	*0.050*
Treatment	1	0.03	0.856
Time	3	11.77	**0.008**
Treatment*Time	3	2.43	0.488
ERV model 2 = 91.9		***42.3***	***0.0002***
Treatment	1	0.26	0.609
Time	3	6.07	0.108
Treatment*Time	3	1.63	0.653
Disease	1	15.49	**0.0001**
Treatment*Disease	1	3.75	0.053
Time*Disease	3	6.80	0.079
Treatment*Time*Disease	3	0.87	0.833
IC model 1 = -12.3		*9.4*	*0.226*
Treatment	1	0.56	0.456
Time	3	7.64	0.054
Treatment*Time	3	1.32	0.725
IC model 2 = -10.5		***38.4***	***0.0008***
Treatment	1	0.37	0.545
Time	3	17.86	**0.0005**
Treatment*Time	3	0.73	0.866
Disease	1	7.44	**0.006**
Treatment*Disease	1	0.17	0.679
Time*Disease	3	14.76	**0.002**
Treatment*Time*Disease	3	3.80	0.284

Table 8-6: Linear mixed models of effect of i) Treatment and Time, or ii) Treatment, Time and Disease on static lung volumes

Treatment represents Intervention (lung volume recruitment, LVR) or Control (active control breathing exercises); Time represents baseline (Time 0a) and final assessment (Time 3a);

Disease indicates motor neurone disease (MND) or other neuromuscular disease (Other); where Treatment, Time and Disease are fixed effects and participant a random effect. *P*-values in **bold** indicate statistically significant values ($p<0.05$).
FRC = Functional residual capacity, RV = Residual volume, TLC = Total lung capacity, ERV = Expiratory reserve volume, IC = Inspiratory

		FRC (L)		RV (L)		TLC (L)	
		Mean difference (95% CI)	***p*-value**	**Mean difference (95% CI)**	***p*-value**	**Mean difference (95% CI)**	***p*-value**
Between group over time							
LVR *vs*. Control	Time 3a – 0a	-0.09 (-0.28, 0.11)	0.383	-0.11 (-0.29, 0.07)	0.237	-0.10 (-0.28, 0.09)	0.292
Within group over time							
Time 3a – 0a	LVR	-0.02 (-0.15, 0.10)	0.695	0.00 (-0.11, 0.10)	0.938	-0.09 (-0.21, 0.03)	0.131
Time 3a – 0a	Control	0.06 (-0.09, 0.21)	0.413	0.11 (-0.04, 0.25)	0.162	0.01 (-0.14, 0.15)	0.924

		ERV (L)		IC (L)	
		Mean difference (95% CI)	***p*-value**	**Mean difference (95% CI)**	***p*-value**
Between group over time					
LVR *vs*. Control	Time 3a – 0a	0.02 (-0.05, 0.10)	0.538	0.01 (-0.08, 0.11)	0.793
Within group over time					
Time 3a – 0a	LVR	-0.02 (-0.08, 0.04)	0.500	-0.05 (-0.11, 0.00)	0.072
Time 3a – 0a	Control	-0.04 (-0.09, 0.00)	0.072	-0.06 (-0.14, 0.01)	0.097

Table 8-7: Summary of the post-hoc comparisons of the effects of regular LVR on static lung volumes, by treatment group.

These data represent observed mean differences (95% confidence intervals) across time and between groups. Time = Timepoint, where Time 3a – 0a = final minus baseline values; LVR = lung volume recruitment group; Control = active control group. *P*-values in **bold** refer to comparisons that were statistically significant on post-hoc testing of raw data ($p<0.05$).

8.7 RESULTS: PRIMARY HYPOTHESIS – COUGH AND MUSCLE STRENGTH

8.7.1 UNASSISTED PEAK COUGH FLOW (PCF)

The models of the effects on PCF of i) treatment and time (p=0.141), and ii) treatment, time and disease (p=0.175) were not significant overall (Table 8-8). There was a main effect of time in both models; the decrease in PCF reached statistical significance on post-hoc exploratory testing in the LVR group (Table 8-9). No statistically significant main effect of disease was identified, however exploratory post-hoc testing suggested an overall reduction in people with MND of -21 (-35, -7) L/min (p=0.005). This decline across the three-months was more so in the MND, LVR sub-group (Table in Appendix 11.5.3), however these PCF changes are purely exploratory given there were no significant model effects.

8.7.2 PEAK COUGH FLOW FROM LIC (PCF_{LIC})

The model representing effects on PCF_{LIC} was significant overall (p=0.031), with a main effect of time (p=0.017) but no treatment or interaction effect noted (Table 8-8, Figure in Appendix 11.5.4). Post-hoc testing suggested a statistically significant increase in PCF_{LIC} over time in the LVR group of 20 (6, 33) L/min (p=0.005). Although no statistically significant increase was seen in the control arm, a between-group difference was not observed (p=0.063) (Table 8-9).

This effect of time was no longer present when disease was included in the model, nor were there any disease or treatment effects (model p=0.021, Table 8-8). However improvement in PCF_{LIC} over the three-months was found in the model for the Other NMD disease type (mean increase 18 (7, 30) L/min, p=0.003), with the Other, LVR sub-group contributing substantially to this (mean increase 27 (9, 44) L/min, p=0.006) (Table in Appendix 11.5.3, Figure in Appendix 11.5.4).

8.7.3 PCF_{LIC} MINUS PCF DIFFERENCE

The model investigating the effect of treatment and time on the PCF_{LIC} – PCF difference was significant overall (p=0.0009), and indicated a main effect of time (Table 8-8). No effect of treatment or interaction effect were found, however post-hoc analyses of observed data showed a statistically significant mean improvement in participants randomised to the LVR intervention of 36 (18, 53) L/min (p=0.0002) as well as a between-group difference after three-months of 25 (2, 49) L/min (p=0.036) (Table 8-9, Figure in Appendix 11.5.4).

When disease was added as a factor, the model remained statistically significant (p=0.004) with an effect of time, plus treatment by disease interaction present (Table 8-8, Figure 8-13). Post-hoc analysis suggested that participants with Other NMDs as a disease group had a significant mean improvement in PCF_{LIC} – PCF of 25 (9, 41) L/min (p=0.002). This increase was statistically significant in the Other, LVR sub-group (37 (13, 62) L/min, p=0.004). An improvement was also found in the MND, LVR sub-group of 32 (13, 51) L/min (p=0.004), suggesting that the increase observed in the LVR intervention was present in both disease types (Table in Appendix 11.5.3).

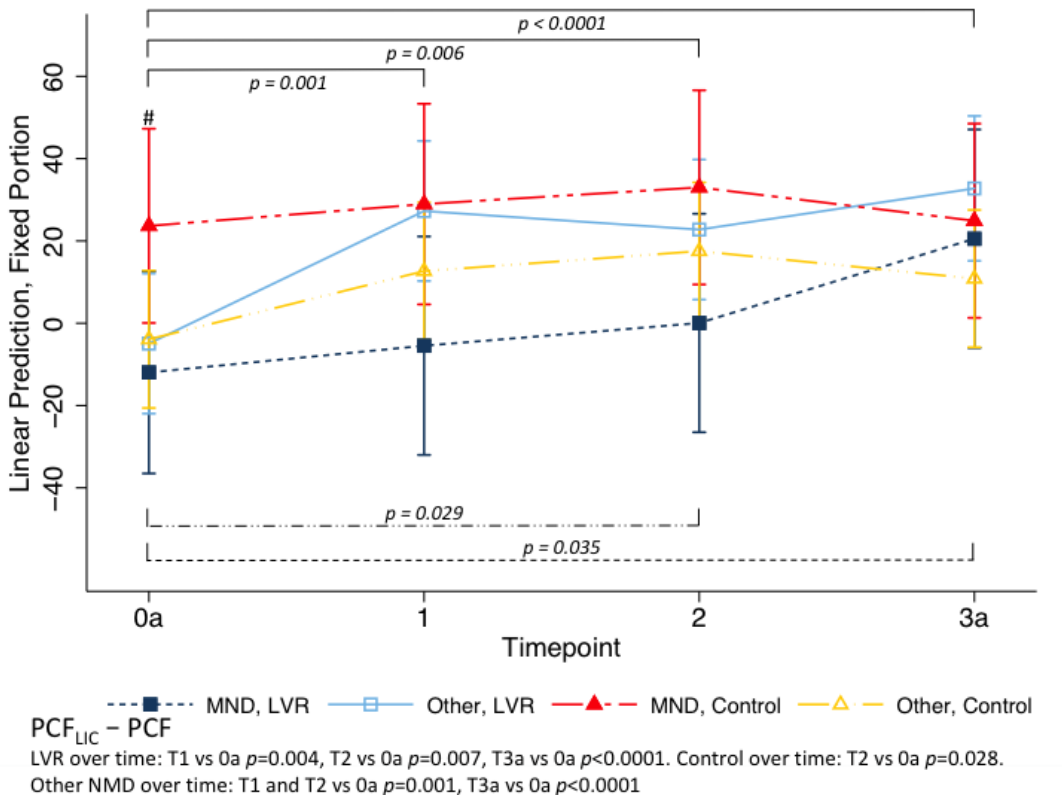

Figure 8-13: Linear mixed model – effects of treatment and time on the PCF_{LIC} – PCF difference, by disease type.

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of treatment and time on peak cough flow from lung insufflation capacity minus peak cough flow (PCF_{LIC} – PCF, L/min) difference, by disease type. ***Model significant, main effect of time and interaction effect between treatment and disease present.*** *P*-values refer to statistically significant comparisons, where # represents statistically significant difference between treatments by disease (MND, LVR vs MND, Control at Time 0a (p=0.040)); and line patterns represent statistically significant differences over time (matching sub-group legend i.e., "Other, LVR", "Other, Control" and "MND, LVR").

Variable model	df	χ^2	*p*-value
PCF model 1: log restricted likelihood = -1471.2		*10.9*	*0.141*
Treatment	1	0.11	0.738
Time	3	8.77	**0.033**
Treatment*Time	3	2.21	0.530
PCF model 2: log restricted likelihood = -1438.6		*19.9*	*0.175*
Treatment	1	0.09	0.763
Time	3	10.21	**0.017**
Treatment*Time	3	4.12	0.249
Disease	1	1.03	0.310
Treatment*Disease	1	0.00	0.980
Time*Disease	3	5.52	0.137
Treatment*Time*Disease	3	2.79	0.426
PCF_{LIC} model 1 = -1447.8		***15.4***	***0.031***
Treatment	1	0.31	0.580
Time	3	10.25	**0.017**
Treatment*Time	3	5.43	0.143
PCF_{LIC} model 2 = -1414.0		***28.1***	***0.021***
Treatment	1	1.08	0.298
Time	3	5.15	0.161
Treatment*Time	3	4.92	0.178
Disease	1	1.17	0.279
Treatment*Disease	1	2.25	0.134
Time*Disease	3	7.34	0.062
Treatment*Time*Disease	3	1.31	0.726
PCF_{LIC} – PCF model 1 = -1486.0		***24.7***	***0.0009***
Treatment	1	0.05	0.832
Time	3	19.95	**0.0002**
Treatment*Time	3	5.40	0.145
PCF_{LIC} – PCF model 2 = -1452.9		***33.3***	***0.004***
Treatment	1	1.20	0.273
Time	3	13.71	**0.003**
Treatment*Time	3	5.27	0.153
Disease	1	0.00	0.983
Treatment*Disease	1	5.92	**0.015**
Time*Disease	3	2.37	0.499
Treatment*Time*Disease	3	0.80	0.848

Variable model	df	χ^2	*p*-value
MIP model 1 = -543.5		*6.9*	*0.074*
Treatment	1	2.95	0.086
Time	1	3.92	**0.048**
Treatment*Time	1	0.04	0.845
MIP model 2 = -528.2		***19.4***	***0.007***
Treatment	1	2.52	0.113
Time	1	9.42	**0.002**
Treatment*Time	1	0.11	0.745
Disease	1	1.27	0.259
Treatment*Disease	1	0.01	0.905
Time*Disease	1	8.29	**0.004**
Treatment*Time*Disease	1	0.91	0.341
SNIP model 1 = -533.8		*2.9*	*0.400*
Treatment	1	2.43	0.119
Time	1	0.01	0.943
Treatment*Time	1	0.45	0.504
SNIP model 2 = -518.3		***16.3***	***0.022***
Treatment	1	2.06	0.151
Time	1	1.31	0.253
Treatment*Time	1	0.56	0.455
Disease	1	5.20	**0.023**
Treatment*Disease	1	0.08	0.775
Time*Disease	1	6.92	**0.009**
Treatment*Time*Disease	1	0.58	0.447
MEP model 1 = -542.9		*2.3*	*0.513*
Treatment	1	0.78	0.377
Time	1	1.09	0.296
Treatment*Time	1	0.54	0.462
MEP model 2 = -523.0		***23.4***	***0.0015***
Treatment	1	1.26	0.262
Time	1	7.97	**0.005**
Treatment*Time	1	0.39	0.532
Disease	1	0.11	0.740
Treatment*Disease	1	0.47	0.494
Time*Disease	1	13.01	**0.0003**
Treatment*Time*Disease	1	6.81	**0.009**

Table 8-8: Linear mixed models of effect of i) Treatment and Time, or ii) Treatment, Time and Disease on cough and respiratory muscle strength

Treatment represents Lung Volume Recruitment or Control; Time represents baseline (Time 0a) and final assessment (Time 3a); Disease indicates motor neurone disease (MND) or other neuromuscular disease (Other); where Treatment, Time and Disease are fixed effects and participant a random effect. *P*-values in **bold** indicate statistically significant values ($p<0.05$).
PCF = peak cough flow, PCF_{LIC} = PCF from lung insufflation capacity, PCF_{LIC} – PCF = PCF_{LIC} minus PCF difference, MIP = Maximal inspiratory pressure, SNIP = Sniff nasal inspiratory pressure, MEP = Maximal expiratory pressure.

		PCF (L/min)		PCF_{LIC} (L/min)		PCF_{LIC} – PCF (L/min)	
		Mean difference (95% CI)	***p*-value**	**Mean difference (95% CI)**	***p*-value**	**Mean difference (95% CI)**	***p*-value**
Between group over time							
LVR *vs.* Control	Time 3a – 0a	-7.5 (-26.3, 11.3)	0.430	17.3 (-0.9, 35.6)	0.063	25.5 (1.7, 49.2)	**0.036**
Within group over time							
Time 3a – 0a	LVR	-15.4 (-25.7, -5.2)	**0.004**	19.6 (6.4, 32.8)	**0.005**	35.7 (18.4, 53.1)	**0.0002**
Time 3a – 0a	Control	-8.0 (-23.4, 7.5)	0.303	2.3 (-10.7, 15.3)	0.723	10.2 (-6.4, 26.9)	0.221

		MIP (cmH_2O)		SNIP (cmH_2O)		MEP (cmH_2O)	
		Mean difference (95% CI)	***p*-value**	**Mean difference (95% CI)**	***p*-value**	**Mean difference (95% CI)**	***p*-value**
Between group over time							
LVR *vs.* Control	Time 3a – 0a	0.3 (-3.5, 4.0)	0.889	1.3 (-3.1, 5.6)	0.566	-1.5 (-6.4, 3.5)	0.556
Within group over time							
Time 3a – 0a	LVR	-1.8 (-4.2, 0.6)	0.144	0.5 (-3.0, 3.9)	0.788	-2.0 (-4.6, 0.7)	0.141
Time 3a – 0a	Control	-2.0 (-4.9, 0.8)	0.154	-0.8 (-3.6, 2.1)	0.574	-0.5 (-4.6, 3.6)	0.810

Table 8-9: Summary of the post-hoc comparisons of the effects of regular LVR on peak cough flow and markers of respiratory muscle strength, by treatment group.

These data represent observed mean differences (95% confidence intervals) across time and between groups. Time = Timepoint, where Time 3a – 0a = final minus baseline values; LVR = lung volume recruitment group; Control = active control group. *P*-values in **bold** refer to comparisons that were statistically significant on post-hoc testing of raw data ($p<0.05$).

8.7.4 MAXIMAL INSPIRATORY PRESSURE (MIP)

The model examining the effect of treatment and time on MIP was not significant overall (p=0.074) but did demonstrate a main effect of time. When disease was included, the model was statistically significant (p=0.007), with a main effect of time, and a disease by time interaction. There was no treatment effect, or treatment by disease and time interaction (Table 8-8).

Post-hoc analysis of the second model identified a reduction in MIP over time in participants with MND (observed mean decrease -6.4 (-10.1, -2.8) cmH_2O, p=0.002). Exploratory post-hoc testing suggested a statistically significant fall in MIP from Timepoint 0a to 3a in the MND, Control sub-group of -7.2 (-12.3, -2.1) cmH_2O (p=0.010), and a non-significant decrease of -5.1 (-11.9, 1.7) cmH_2O in the MND, LVR sub-group (p=0.115). Participants with Other NMDs remained stable regardless of treatment (Table in Appendix 11.5.3)

8.7.5 SNIFF NASAL INSPIRATORY PRESSURE (SNIP)

The model analysing the effect of treatment and time on SNIP was not significant for the cohort as a whole (Table 8-8). Similar to the findings for MIP however, the model including disease was statistically significant (p=0.022). No effect of treatment on SNIP was identified, with the magnitude of change observed over time in the LVR group compared to Control group not statistically different (group mean difference = 1.3 (-3.1, 5.6) cmH_2O, p=0.566) (Table 8-9).

However, a main effect of disease and a disease by time interaction were observed, with the MND disease group declining over time (group mean difference = -4.8 (-7.3, -2.2) cmH_2O, p=0.0009). Although no treatment effects were observed, on exploratory post-hoc analysis the MND, Control group demonstrated a statistically significant decrease over time (mean difference = -6.0 (-8.9, -3.1) cmH_2O, p=0.008), whereas the MND, LVR sub-group remained stable (mean difference = -2.9 (-8.3, 2.4) cmH_2O, p=0.235). There was no statistical difference in this degree of change between-groups

by disease type (MND p=0.223). A between disease-type difference was found at Timepoint 3a (MND *vs.* Other NMD, p=0.011), likely due to this decline in participants with MND (Table in Appendix 11.5.3).

8.7.6 MAXIMAL EXPIRATORY PRESSURE (MEP)

As per the markers of inspiratory muscle strength, the model investigating the effect of treatment and time on MEP was not significant for the group as a whole (Table 8-8). When disease type was included as a factor, there was a statistically significant effect for the model (p=0.002), with a main effect of time, a disease by time interaction, and a disease, time and treatment interaction (Table 8-8, Figure 8-14).

The magnitude of change observed over time as a whole cohort was not different between-groups (p=0.556) (Table 8-9). However, a statistically significant reduction in MEP of -8.0 (-11.3, -4.7) cmH_2O (p=0.0001) was observed in participants with MND, with both the MND, LVR and MND, Control sub-groups declining (Table in Appendix 11.5.3). Post-hoc exploratory analysis suggested that the decline was greater in the MND, Control group (MND, LVR minus MND, Control mean difference = 8.1 (2.9, 13.2) cmH_2O, p=0.005). Although baseline values appear higher compared to the MND, LVR arm (55.0 (30.2, 79.8) cmH_2O *vs.* 44.8 (29.3, 60.2) cmH_2O, p=0.408), this difference was not statistically significant.

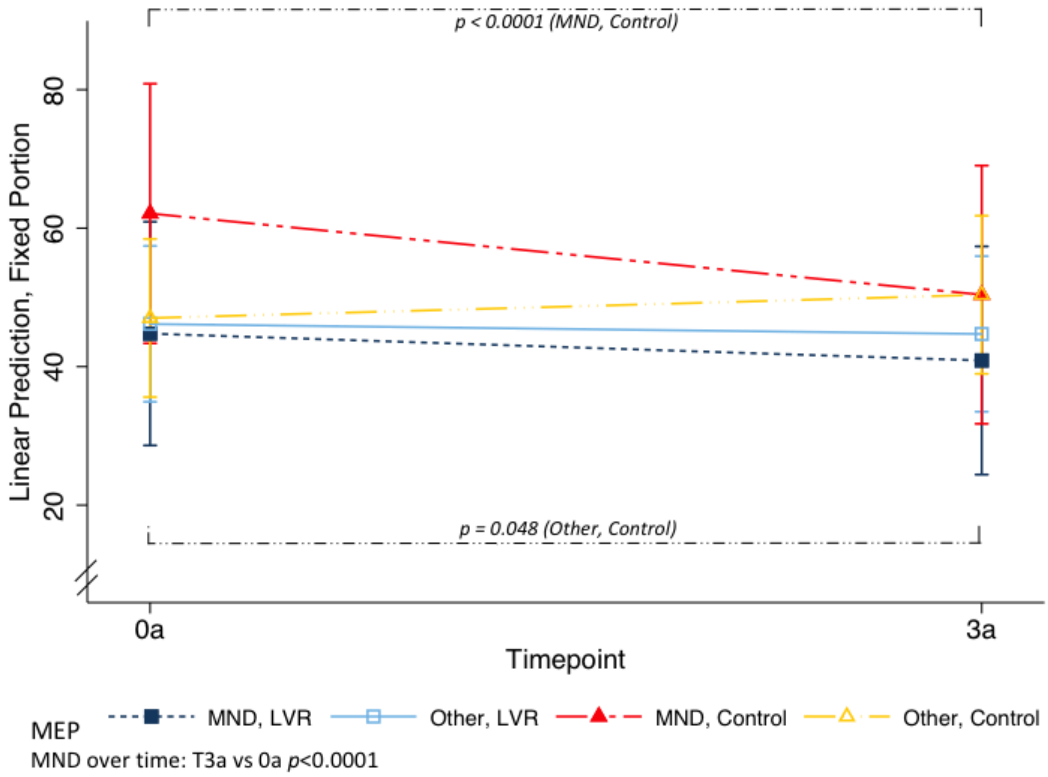

Figure 8-14: Linear mixed model – effects of treatment and time on MEP, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of treatment and time on maximal expiratory pressure (MEP, cmH_2O), by disease type**. *Model significant, main effect of time and interaction effects between time and disease, and treatment, time and disease present*.** *P*-values refer to statistically significant comparisons, where line patterns represent statistically significant difference over time (matching sub-group legend i.e., "MND, Control", "Other, Control").

8.8 SUMMARY OF LINEAR MIXED MODEL FINDINGS

Variable	Significant Effect/s				Between-treatment group (change over time)	Within-treatment group comparisons					
						All		MND		Other	
	Treatment	Time	Disease	Interaction		LVR	Control	LVR	Control	LVR	Control
LIC			Dx	**Rx * T**	**LVR > Control**	↑	-	-	↓	-	-
VC		T	Dx	Dx * T	-	↓	↓	↓	↓	-	-
LIC – VC				**Rx * T**	**LVR > Control**	↑	-	↑	-	-	-
C_{rs}		T	Dx		-	↑	-	↑	-	-	-
Specific C_{rs}		T			-	↑	-	-	-	↑	-
FRC			Dx		-	-	-	-	-	-	-
RV			Dx		-	-	-	-	-	-	-
TLC			Dx		-	-	-	-	-	-	-
ERV			Dx		-	-	-	-	-	-	-
IC		T	Dx	Dx * T	-	-	-	↓	↓	-	-
PCF		T			-	↓	-	↓	-	-	-
PCF_{LIC}		T			-	↑	-	-	-	↑	-
PCF_{LIC} – PCF		T		Rx * Dx	**MND, LVR > MND, Control**	↑	↑	↑	-	↑	↑
MIP		T		Dx * T	-	-	-	-	↓	-	-
SNIP			Dx	Dx * T	-	-	-	-	↓	-	-
MEP		T		Dx * T Rx * Dx * T	**MND, LVR < MND, Control**	-	-	-	↓	-	↑

Table 8-10: Summary of RCT findings: Effects on respiratory function, by treatment, time and disease

Bold variable name indicates Model 1 (Treatment, Time) statistically significant overall; *Italic* variable name indicates Model 2 (Treatment, Time, Disease) statistically significant overall; ***Bold & italic*** variable name indicates both Models statistically significant overall. Models for C_{rs} and PCF were not significant.

Main effects of Treatment (Rx) and Disease (Dx) are between-group differences. Main effect of Time (T) indicates within-group change over time. Interaction effects indicated by Rx * T, Dx * T, Rx * Dx or Rx * Dx *T.

LVR = lung volume recruitment, Control = active control arm, MND = motor neurone disease, Other = other neuromuscular disease .

Between-treatment group indicates the nature of the treatment effect over time as noted on the linear mixed models.

Within-treatment group refers to change over time within-groups as noted on the linear mixed models.

Arrows = increase or decrease in group mean, "-" indicates no significant change.

8.9 RESULTS: HEALTH-RELATED QUALITY OF LIFE

8.9.1 ASSESSMENT OF QUALITY OF LIFE (AQOL-8D)

Summary statistics for each of the eight domains, total AQoL-8D profile scores and utility scores are provided in Appendix 11.5.3.

No change in psychometric generic HRQoL was observed in either group (linear mixed model p=0.642, Table 8-11). Likewise, models for the unweighted domains Happiness, Senses, Pain, Mental Health, Self Worth, Coping or Relationships were not significant (data not shown).

The model for the Independent Living domain was significant overall (p=0.007) and indicated a main effect of time (Table 8-11). No effects of treatment or interaction were present. Post-hoc analysis suggested a decline in the Control group may be contributing to the change over time, with a mean change of -6.79 (-11.55, -2.03) units (paired t-test p=0.007). The LVR group remained stable (-1.61 (-5.34, 2.11) units, p=0.384), and no significant between-group difference in change over time was found (LVR minus Control = 5.18 (-0.90, 11.25) units, p=0.094).

Weighted AQoL-8D utility scores for each of the eight dimensions, two super-dimensions and the overall AQoL-8D utility index were also computed. As per the psychometric measure, there were no effects on overall health state utility within or between the treatments, either as a whole group of people with NMD or by disease types (Table 8-11) (Figures in Appendix 11.5.4).

There were no significant effects for the super-dimension models of Physical Health, Psychosocial Health, or seven of the eight dimensions (Appendix 11.5.4). A main effect of time was found in the Happiness health state utility, although the model was not significant overall. When disease type was added to the model a statistically significant effect was identified, with a main effect of time and disease by time interaction (Table 8-11). Declines in participants with MND; the LVR group; MND, Control and Other, LVR

sub-groups may be contributing, although no treatment or interaction effects were observed (Figure in Appendix 11.5.4).

Variable model	χ^2	*p*-value
AQoL-8D unweighted total score Model 1: log restricted likelihood = -478.6	*1.7*	*0.642*
Treatment	0.29	0.593
Time	1.37	0.242
Treatment*Time	0.01	0.929
AQoL-8D Independent Living domain Model 1 = -587.9	***12.0***	***0.007***
Treatment	0.42	0.518
Time	7.22	**0.007**
Treatment*Time	3.55	0.059
AQoL-8D weighted Utility Index Model 1 = 85.0	*1.5*	*0.676*
Treatment	0.44	0.507
Time	0.02	0.881
Treatment*Time	1.05	0.305
AQoL-8D weighted Utility Index Model 2 = 79.2	*7.6*	*0.365*
Treatment	0.83	0.362
Time	0.67	0.413
Treatment*Time	0.25	0.619
Disease	0.18	0.674
Treatment*Disease	0.76	0.384
Time*Disease	2.96	0.085
Treatment*Time*Disease	1.49	0.223
AQoL-8D Physical Health Super Dimension Model 1 = 98.2	*1.2*	*0.756*
Treatment	0.45	0.503
Time	0.61	0.436
Treatment*Time	0.07	0.787
AQoL-8D Psychosocial Health Super Dimension Model 1 = 83.8	*1.9*	*0. 603*
Treatment	0.40	0.529
Time	0.02	0.879
Treatment*Time	1.42	0.233

Variable model	χ^2	*p*-value
AQoL-8D Happiness Utility Model 1 = 109.2	*7.4*	*0.060*
Treatment	0.66	0.418
Time	4.39	**0.036**
Treatment*Time	2.69	0.101
AQoL-8D Happiness Utility Model 2 = 103.8	*16.6*	***0. 020***
Treatment	0.94	0.333
Time	8.26	**0.004**
Treatment*Time	1.06	0.304
Disease	0.00	0.954
Treatment*Disease	0.48	0.490
Time*Disease	5.19	**0.023**
Treatment*Time*Disease	1.94	0.164

Table 8-11: Linear mixed models of effect of i) Treatment and Time, or ii) Treatment, Time and Disease on Health-related quality of life

Treatment represents Lung Volume Recruitment or Control; Time represents baseline (Time 0a) and final assessment (Time 3a); Disease indicates motor neurone disease (MND) or other neuromuscular disease (Other); where Treatment, Time and Disease are fixed effects and participant a random effect. *P*-values in **bold** indicate statistically significant values ($p<0.05$). AQoL-8D = Assessment of quality of life with 8 domains.

8.9.2 SEVERE RESPIRATORY INSUFFICIENCY QUESTIONNAIRE (SRI)

Analysis of the SRI summary scale found no significant effect of treatment over time. Whilst a main effect of time and a disease by time interaction were observed when disease was included in the model, the model overall remained insignificant (Table 8-12). Exploratory post-hoc tests suggested there may be an improvement in participants with MND over time (mean difference 4.9 (1.1, 8.6) units, *p*=0.013), regardless of treatment (Figure 8-15).

A statistically significant treatment by time interaction effect was identified in the Social Functioning domain. Furthermore, when disease was included in the model, a main effect of time, disease by time and treatment by time interactions were found (Table 8-12, Figure 8-16). Post-hoc exploratory analysis of the observed data did not support the model findings: change over time in participants with MND (mean difference 4.7 (-2.8, 12.2) units, *p*=0.204), the Control arm (mean difference 1.5 (-3.5, 6.5) units, *p*=0.547), and the MND, Control sub-group (mean difference 7.1 (-6.1, 20.2) units, *p*=0.266) were not statistically significant.

Models examining the effects of time or treatment on the other SRI sub-scales were not significant (Table 8-12). Although an improvement in the Respiratory complaint sub-scale was observed on post-hoc comparison in participants with MND (mean difference 7.7 (0.3, 15.1) units, *p*=0.041), the model was not significant. A main effect of disease was however found in the Physical Functioning sub-scale; participants with MND demonstrated lower scores than those with Other NMDs at both Timepoint 0a (mean difference -8.7 (-14.5, -2.8) units, *p*=0.004) and Timepoint 3a (mean difference -9.6 (-14.4, -4.8) units, *p*=0.0002) regardless of treatment (Table 8-12).

Variable model	**χ^2**	***p*-value**
SRI summary scale ***Model 1: log restricted likelihood = -501.7***	*2.9*	*0.412*
Treatment	0.00	0.997
Time	2.65	0.104
Treatment*Time	0.12	0.727

Variable model	χ^2	*p*-value
SRI summary scale Model 2 = -491.1	*9.3*	*0.230*
Treatment	0.06	0.811
Time	6.27	**0.012**
Treatment*Time	0.01	0.942
Disease	0.04	0.849
Treatment*Disease	0.28	0.598
Time*Disease	5.99	**0.014**
Treatment*Time*Disease	0.11	0.742
SRI Social Functioning sub-scale Model 1 = -563.3	***9.3***	***0.025***
Treatment	0.62	0.432
Time	2.64	0.104
Treatment*Time	5.43	**0.020**
SRI Social Functioning sub-scale Model 2 = -546.6	*27.0*	***0. 0003***
Treatment	0.68	0.409
Time	9.23	**0.002**
Treatment*Time	5.10	**0.024**
Disease	2.38	0.123
Treatment*Disease	0.00	0.996
Time*Disease	13.22	**0.0003**
Treatment*Time*Disease	0.20	0.652
SRI Physical Functioning sub-scale Model 1 = -560.9	*1.9*	*0.592*
Treatment	0.73	0.393
Time	0.58	0.448
Treatment*Time	0.60	0.440
SRI Physical Functioning sub-scale Model 2 = -542.6	*22.4*	***0. 002***
Treatment	0.70	0.402
Time	0.37	0.546
Treatment*Time	1.17	0.280
Disease	17.72	**<0.0001**
Treatment*Disease	0.13	0.714
Time*Disease	0.02	0.890
Treatment*Time*Disease	1.57	0.211

Variable model	χ^2	*p*-value
SRI Respiratory Complaints sub-scale Model 1 = -611.8	*2.3*	*0.509*
Treatment	0.22	0.639
Time	2.12	0.145
Treatment*Time	0.04	0.842
SRI Symptoms and Sleep sub-scale Model 1 = -552.2	*1.2*	*0.754*
Treatment	0.01	0.919
Time	1.06	0.302
Treatment*Time	0.07	0.788
SRI Psychological Wellbeing sub-scale Model 1 = -519.9	*3.1*	*0.383*
Treatment	1.06	0.304
Time	0.36	0.549
Treatment*Time	1.50	0.221
SRI Social Relationships sub-scale Model 1 = -565.7	*1.4*	*0.704*
Treatment	0.49	0.482
Time	0.94	0.332
Treatment*Time	0.00	0.996
SRI Anxiety sub-scale Model 1 = -628.7	*1.6*	*0.665*
Treatment	0.09	0.767
Time	0.87	0.352
Treatment*Time	0.51	0.475

Table 8-12: Linear mixed models of effect of i) Treatment and Time, or ii) Treatment, Time and Disease on Disease-specific quality of life and respiratory symptoms

Treatment represents Lung Volume Recruitment or Control; Time represents baseline (Time 0a) and final assessment (Time 3a); Disease indicates motor neurone disease (MND) or other neuromuscular disease (Other); where Treatment, Time and Disease are fixed effects and participant a random effect. *P*-values in **bold** indicate statistically significant values ($p<0.05$). SRI = Severe Respiratory Insufficiency questionnaire.

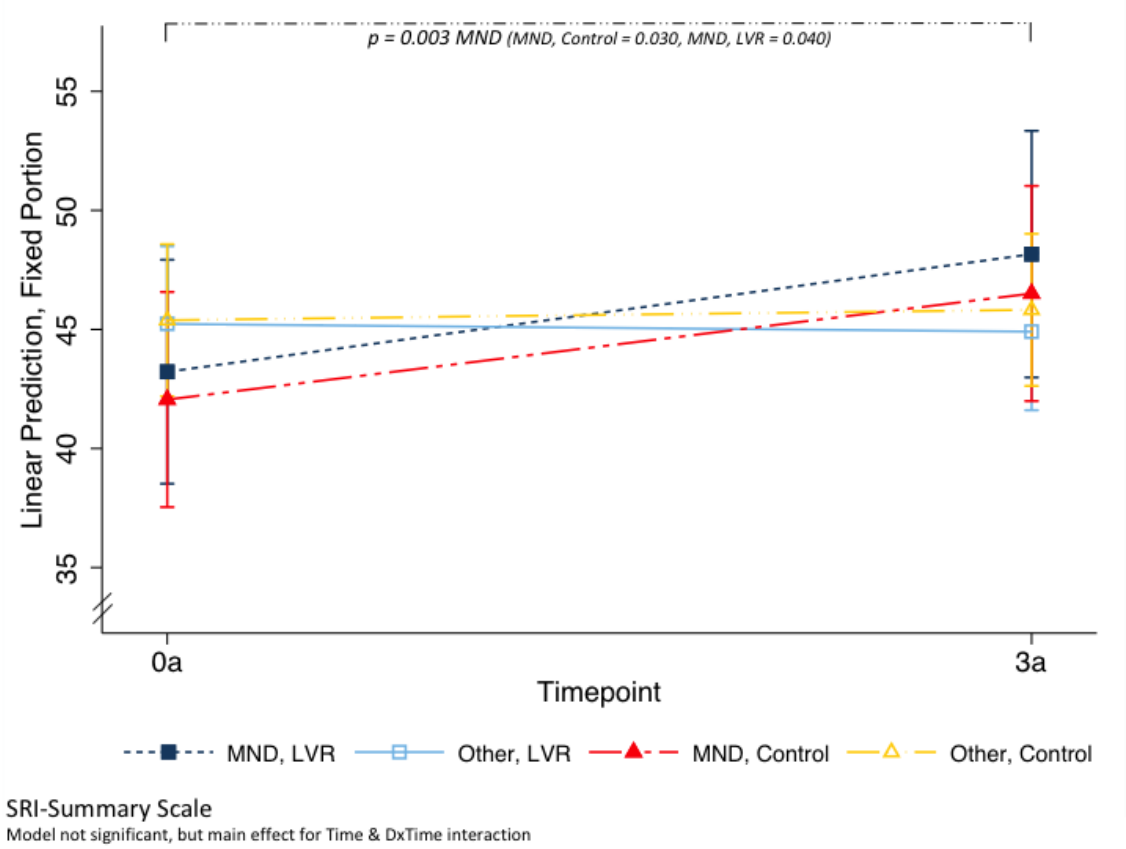

Figure 8-15: Linear mixed model – effects of treatment and time on the SRI Summary scale, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of treatment and time on the SRI Summary scale, by disease type. ***Model not significant however main effect of time and disease by time interaction present.*** *P*-values refer to statistically significant comparisons between the estimated margins, where line represents statistically significant improvement over time in participants with MND

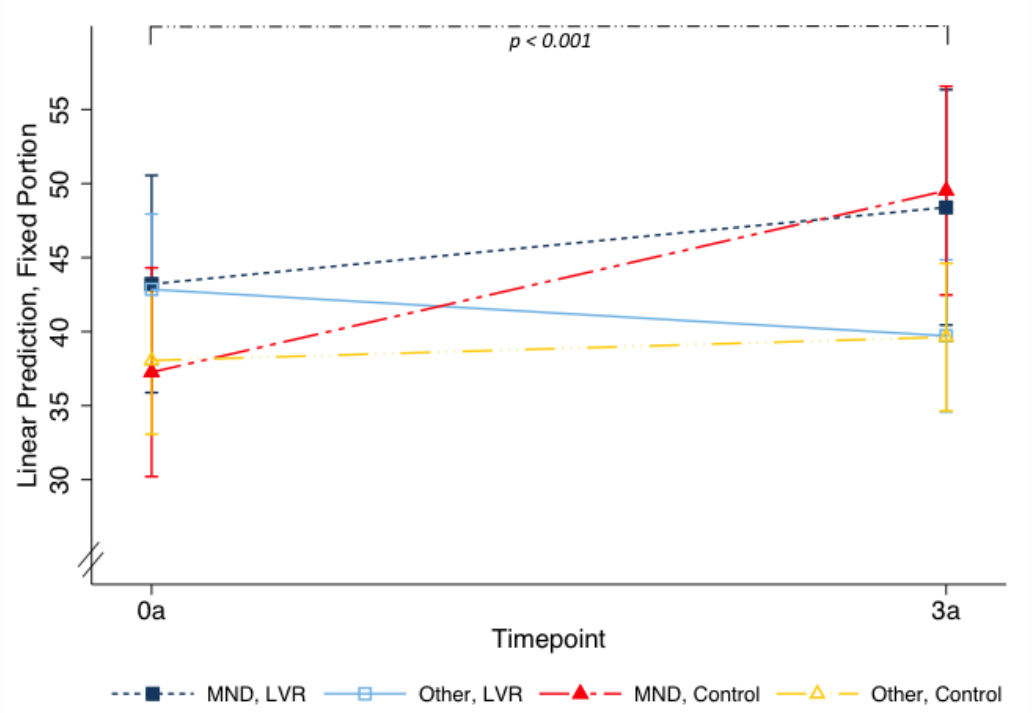

Figure 8-16: Linear mixed model – effects of treatment and time on the SRI Social Functioning sub-scale, by disease type

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of treatment and time on the SRI Social Functioning sub-scale, by disease type. ***Model significant, main effect of time, treatment by time and disease by time interactions present.*** *P*-values refer to statistically significant comparisons between the estimated margins, where line represents statistically significant improvement over time in participants in the MND, Control arm.

8.9.3 ALSFRS FUNCTIONAL RATING SCALE (ALSFRS-R)

A statistically significant effect of time was found in the ALSFRS-R summary score, with values declining over the three-month study period (Table 8-13, Figure 8-17). The observed reduction in the LVR group was 4.5 (2.1 to 6.9) points, and 6.3 (2.9 to 9.7) in the Control arm (both p=0.002), with no significant between-group difference in the magnitude of this decline (p=0.379).

Similarly, models of the Bulbar, Fine Motor and Gross Motor function sub-scores were significant, with all demonstrating decline over time (Table 8-13). In the Bulbar and Fine motor sub-scores, this reduction appeared to be in both groups, whereas for Gross Motor function, this was predominantly due to a fall in the Control group (summary statistics in Appendix 11.5.3). However, no interaction effects or between-group differences were found for any of these ALSFRS-R variables. No model effects were identified for the ALSFRS-R Respiratory sub-score (Table 8-13).

Variable model	χ^2	*p*-value
ALSFRS-R summary score Model log restricted likelihood = -142.9	***32.4***	***< 0.0001***
Treatment	2.80	0.095
Time	26.96	**<0.0001**
Treatment*Time	1.21	0.272
ALSFRS-R bulbar sub-score Model log restricted likelihood = -106.2	***21.6***	***0.0001***
Treatment	0.87	0.351
Time	20.66	**<0.0001**
Treatment*Time	0.01	0.904
ALSFRS-R fine motor sub-score Model log restricted likelihood = -115.3	***13.3***	***0.004***
Treatment	0.00	0.989
Time	12.39	**0.0004**
Treatment*Time	0.25	0.616
ALSFRS-R gross motor sub-score Model log restricted likelihood = -107.2	***20.1***	***0.0002***
Treatment	0.33	0.564
Time	14.51	**0.0001**
Treatment*Time	3.21	0.073
ALSFRS-R respiratory sub-score Model log restricted likelihood = -110.3	*7.0*	*0.071*
Treatment	2.80	0.094
Time	3.86	0.050
Treatment*Time	0.22	0.642

Table 8-13: Linear mixed models of effect of i) Treatment and Time on functional status in participants with MND

Treatment represents Lung Volume Recruitment or Control; Time represents baseline (Time 0a) and final assessment (Time 3a); where Treatment and Time are fixed effects and participant a random effect. *P*-values in **bold** indicate statistically significant values ($p<0.05$). ALSFRS-R = Revised amyotrophic lateral sclerosis functional rating scale.

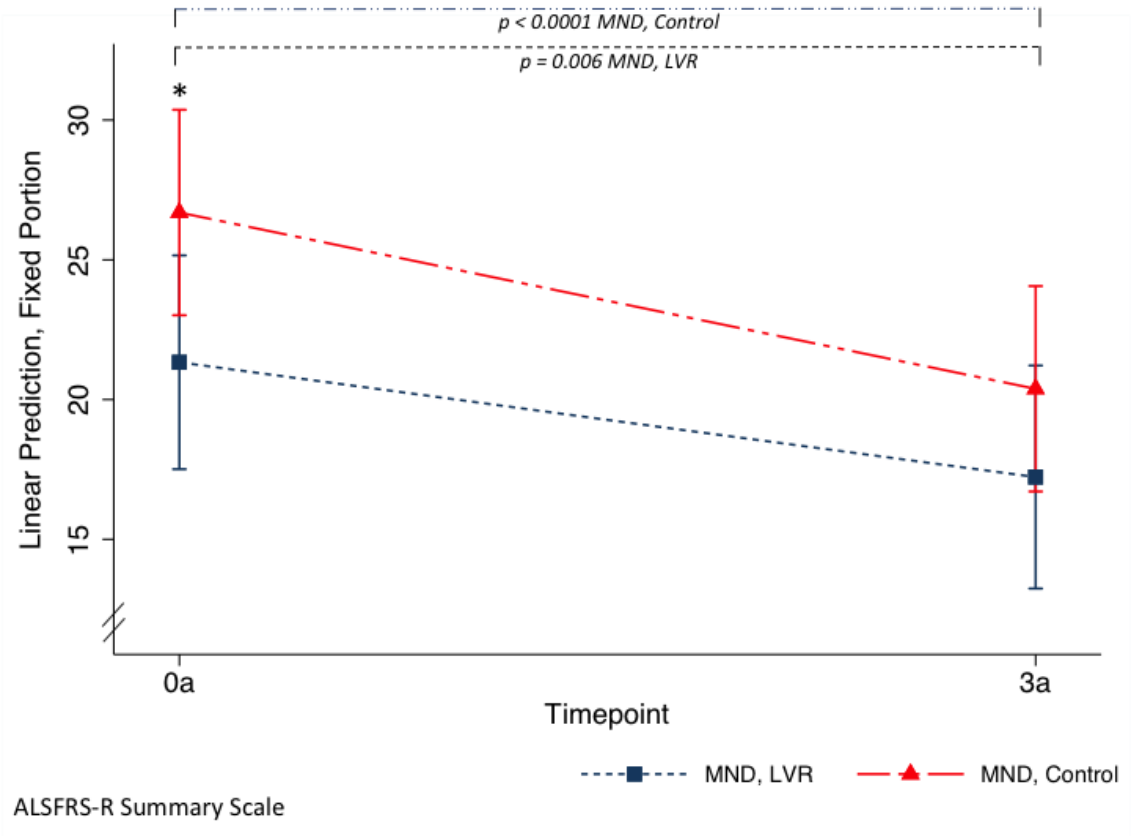

Figure 8-17: Linear mixed model – effects of treatment and time on the ALSFRS-R Summary score

Linear mixed model illustrating the estimated mean (95%CI) marginal effects of treatment and time on the ALSFRS-R Summary score, for participants with MND. ***Model significant and main effect of time present.*** *P*-values refer to statistically significant comparisons between the estimated margins, where * represents differences between treatments (LVR vs Control) at Time 0a (p=0.048), and lines represent statistically significant decline over time in the treatment groups. MND, LVR = motor neurone disease and lung volume recruitment sub-group; MND, Control = motor neurone disease and active control sub-group.

8.10 RESULTS: DOSE-RESPONSE

The relationship between self-reported therapy use (average sessions/day) and observed change in respiratory function over the course of the study duration was explored for the primary (LIC) and secondary outcome measures (VC, LIC-VC, C_{rs}, FRC and TLC). Dose-response analyses were not conducted on HRQoL outcomes given the absence of a treatment effect on summary scores. Associations are illustrated for LIC (Figure 8-18) and C_{rs} (Figure 8-19) and are representative of the absence of association between any of the stated outcomes and dose (Table 8-14).

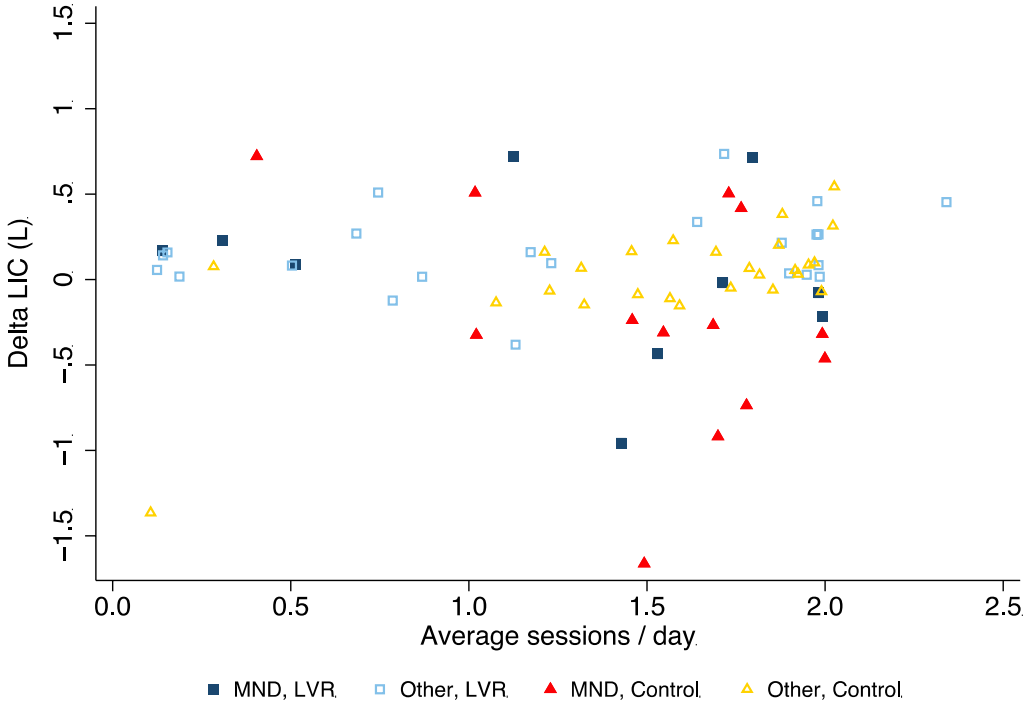

Figure 8-18: Correlation between self-reported average number of therapy sessions / day and change in LIC over the study duration

LIC = lung insufflation capacity (litres), LVR = lung volume recruitment, Control = active control, MND = motor neurone disease, Other = other neuromuscular disease. Average number of therapy sessions per day for both treatment groups was determined from participant self-report diaries.

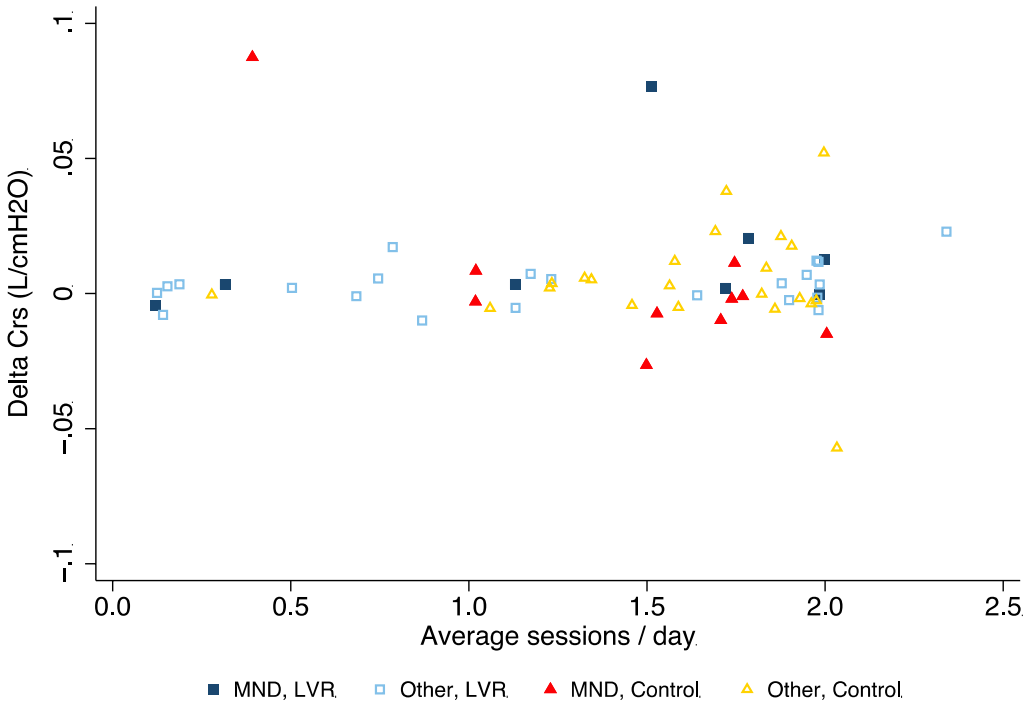

Figure 8-19: Correlation between self-reported average number of therapy sessions / day and change in C_{rs} over the study duration

C_{rs} = respiratory system compliance (litres per centimetres of water), LVR = lung volume recruitment, Control = active control, MND = motor neurone disease, Other = other neuromuscular disease. Average number of therapy sessions per day for both treatment groups was determined from participant self-report diaries.

To confirm that respiratory function change was not associated with LVR use, the duration participants performed LVR was also analysed. The average therapy session lasted 10 minutes (range = 1 min 2 sec to 35 min 41 sec, median = 7 min 18 sec). Overall, participants in the LVR arm performed a mean of 7 minutes, 12 seconds therapy per day (minimum = 1 second, maximum = 22 min 51 secs, median = 4 min 21 sec). No relationship was found between dose and observed change in respiratory function (Table 8-14).

		n	Average sessions/day – diary			Average sessions/day – LVR counter			Average minutes/day		
			Pearson's r	Adj R^2	*p*-value	Pearson's r	Adj R^2	*p*-value	Pearson's r	Adj R^2	*p*-value
Δ LIC	**All**	72	0.04	-0.01	0.718						
	LVR	33	0.06	-0.03	0.732	0.05	-0.03	0.764	0.00	-0.03	0.992
	Control	39	0.15	0.0	0.358						
Δ VC	**All**	73	-0.03	-0.01	0.818						
	LVR	34	-0.06	-0.03	0.747	0.05	0.00	0.994	0.15	-0.01	0.392
	Control	39	0.03	-0.03	0.855						
Δ LIC-VC	**All**	72	0.04	-0.01	0.742						
	LVR	33	0.06	-0.03	0.760	0.02	-0.03	0.931	-0.13	-0.01	0.469
	Control	39	0.15	0.00	0.353						
Δ C_{rs}	**All**	62	-0.02	-0.02	0.858						
	LVR	30	0.25	0.03	0.180	0.17	0.00	0.362	0.05	-0.03	0.800
	Control	32	-0.19	0.05	0.109						
Δ FRC	**All**	57	-0.02	-0.02	0.886						
	LVR	27	0.25	-0.04	0.818	-0.02	-0.04	0.926	-0.18	-0.01	0.360
	Control	30	-0.19	-0.03	0.851						
Δ TLC	**All**	57	0.10	-0.01	0.482						
	LVR	27	0.04	-0.04	0.837	0.04	-0.04	0.848	-0.11	-0.03	0.594
	Control	30	0.10	-0.02	0.584						

Table 8-14: Univariate analysis of change in respiratory function parameters over the three-month RCT and therapy use

Delta values (Δ) defined as Timepoint 3a minus 0a. LIC = lung insufflation capacity, VC = vital capacity, LIC – VC = lung insufflation capacity minus vital capacity difference, C_{rs} = respiratory system compliance, FRC = functional residual capacity, TLC = total lung capacity, LVR = lung volume recruitment, Control = active control arm. Therapy use (average number of sessions performed per day of study) was determined from participant self-report diary for both treatment groups. For the LVR arm, use was also derived from the LVR counter and expressed as average therapy sessions per day, and average minutes of LVR therapy per day. n = number of participants with data, *p*-value refers and Pearson's r refers to Pearson's correlation coefficient, Adj R^2 = adjusted R^2. No correlations were statistically significant (all values $p>0.05$).

8.11 SIDE EFFECTS, ADVERSE EVENTS & HOSPITAL PRESENTATIONS

No adverse events were reported over the study duration (6809 participant days), however 29% of this cohort did report side effects of their allocated treatment. These were collated and categorised by theme; musculoskeletal (e.g., muscle soreness or cramping, mild discomfort of the chest wall or stretching sensation), dizziness (and/or light-headedness, "giddy" sensation), shortness of breath, or Other miscellaneous.

No significant difference was found between intervention and control group participants reporting side effects (LVR group = 13 out of 37 participants; Control group = 9 out of 39 participants; Fisher's exact test p=0.772). The most common side effect reported in the LVR group was dizziness (6 participants), followed by musculoskeletal discomfort (n=5), whereas participants performing breathing exercises reported musculoskeletal symptoms and shortness of breath (each n=4). Two participants in the LVR group and one participant in the Control arm reported more than one side effect throughout the study duration (Table in Appendix 11.5.5).

All side effects, with the exception of one participant in the LVR group who withdrew from the study, were intermittent, resolved or were managed by modifying therapy. Strategies included decreasing breath size, number of repetitions or increasing rest duration between sets. One participant with MND performing LVR reported a sore throat during insufflation (categorised as Other miscellaneous), which improved by performing slower bag compressions.

Excessive saliva and fatigue contributed to study withdrawal for one participant with MND performing LVR. This participant had bulbar-onset MND, with severe bulbar dysfunction (ALFRS-R bulbar sub-score = 0) and preserved peripheral limb strength. Whilst they could achieve a LIC > VC by using an oro-nasal mask (Timepoint 0a LIC = 3.78 L, VC = 1.70 L) they felt that LVR forced oral secretions towards their lungs, making it harder to clear and exacerbating the frequency of choking episodes throughout the day. Furthermore, they felt that LVR did not subjectively improve their lung capacity and that deep breathing was just as effective.

The number of participants reporting primary-care or hospital presentations was not significantly different between the treatment groups (LVR = 7 out of 37 participants; Control = 8 out of 39 participants; Fisher's exact test *p*=0.696). Two participants presented to hospital for a RTI / pneumonia over the 6809 participant days; both had an Other NMD diagnosis and were in the LVR (n=1) and Control (n=1) groups. Two participants in the LVR arm (one MND, one Other NMD) presented to hospital twice for non-respiratory issues (Table in Appendix 11.5.5).

8.12 RESULTS: IMMEDIATE EFFECT OF LVR ON RESPIRATORY FUNCTION AFTER THREE-MONTHS

Results of the linear mixed models of the immediate effect of a single-session of LVR at Timepoint 3 (final study visit), by disease type (MND *vs.* Other NMD) and RCT treatment group (LVR *vs.* Control) are presented in Table 8-15.

Models for C_{rs} and LIC were statistically significant, with main effects of disease identified. Participants with MND demonstrated higher C_{rs} and LIC values pre and post the single-session of LVR compared to participants with Other NMD, however there were no effects of time or treatment group (Figures in Appendix 11.5.6).

Static lung volumes demonstrated main effects of time and disease (Table 8-15). Participants with MND had higher lung volumes, which fell after the single-session of LVR regardless of treatment group (Figures in Appendix 11.5.6). A main effect of time was also observed for the PCF model; there was a statistical significant reduction in the LVR and Other NMD sub-groups, however no treatment or disease effects were found (Table 8-15, Figure in Appendix 11.5.6).

Models for VC, LIC – VC difference, specific C_{rs}, PCF_{LIC} and PCF_{LIC} – PCF difference were not significant overall, despite some suggesting main effects (Table 8-15). Notably, none of these were effects over time.

Variable model	**χ^2**	***p*-value**
LIC model: log restricted likelihood = -100.9	***18.5***	***0.010***
Treatment	0.28	0.599
Time	1.15	0.285
Treatment*Time	0.12	0.731
Disease	13.10	**0.0003**
Treatment*Disease	0.02	0.876
Time*Disease	3.14	0.077
Treatment*Time*Disease	0.83	0.364

Variable model	χ^2	*p*-value
VC model = -50.4	*13.7*	*0.058*
Treatment	1.37	0.243
Time	1.31	0.252
Treatment*Time	0.52	0.472
Disease	2.27	0.132
Treatment*Disease	0.86	0.355
Time*Disease	5.94	**0.015**
Treatment*Time*Disease	0.69	0.407
LIC – VC model = -50.6	*11.1*	*0.135*
Treatment	0.00	0.977
Time	0.02	0.884
Treatment*Time	0.56	0.453
Disease	10.02	**0.002**
Treatment*Disease	0.75	0.386
Time*Disease	1.24	0.265
Treatment*Time*Disease	0.03	0.862
C_{rs} model = 317.4	***14.3***	***0.046***
Treatment	0.15	0.695
Time	1.01	0.314
Treatment*Time	0.06	0.809
Disease	12.84	**0.0003**
Treatment*Disease	0.63	0.426
Time*Disease	0.60	0.438
Treatment*Time*Disease	0.43	0.512
Specific C_{rs} model = 220.0	*4.2*	*0.757*
Treatment	0.18	0.675
Time	1.02	0.312
Treatment*Time	0.38	0.538
Disease	1.60	0.206
Treatment*Disease	0.00	0.986
Time*Disease	1.63	0.201
Treatment*Time*Disease	0.24	0.628
FRC model = -55.3	***48.8***	***< 0.0001***
Treatment	0.81	0.369
Time	19.59	**<0.0001**
Treatment*Time	1.02	0.312

Variable model		χ^2	*p*-value
	Disease	21.79	**<0.0001**
	Treatment*Disease	0.69	0.408
	Time*Disease	14.20	**0.0002**
	Treatment*Time*Disease	0.50	0.481
TLC model = -76.8		***33.8***	***< 0.0001***
	Treatment	0.58	0.447
	Time	8.08	**0.005**
	Treatment*Time	0.01	0.935
	Disease	20.75	**<0.0001**
	Treatment*Disease	0.99	0.319
	Time*Disease	4.13	**0.042**
	Treatment*Time*Disease	0.01	0.942
RV model = -35.4		***26.8***	***0.0004***
	Treatment	1.14	0.286
	Time	4.40	**0.036**
	Treatment*Time	0.33	0.566
	Disease	17.90	**<0.0001**
	Treatment*Disease	0.24	0.624
	Time*Disease	1.65	0.200
	Treatment*Time*Disease	0.53	0.467
PCF model = -669.7		***14.6***	***0.042***
	Treatment	1.97	0.161
	Time	7.76	**0.005**
	Treatment*Time	1.07	0.301
	Disease	0.20	0.654
	Treatment*Disease	0.11	0.740
	Time*Disease	0.18	0.671
	Treatment*Time*Disease	0.03	0.858
PCF_{LIC} model = -667.9		*5.1*	*0.653*
	Treatment	0.14	0.707
	Time	0.51	0.473
	Treatment*Time	0.20	0.653
	Disease	0.31	0.575
	Treatment*Disease	0.34	0.559
	Time*Disease	0.01	0.935
	Treatment*Time*Disease	3.32	0.069

Variable model	χ^2	*p*-value
PCF_{LIC} – PCF model = -644.1	*11.5*	*0.120*
Treatment	3.97	**0.046**
Time	1.11	0.292
Treatment*Time	1.84	0.175
Disease	0.02	0.884
Treatment*Disease	0.16	0.690
Time*Disease	0.45	0.501
Treatment*Time*Disease	2.92	0.087

Table 8-15: Linear mixed models of effect of i) Time, Disease and Treatment on respiratory function in participants with neuromuscular disease, not naïve to LVR

Time represents pre and post a single-session of LVR, Disease represents MND or Other NMD, and Treatment indicates participants randomised to regular LVR or Active Control for the three-month RCT period.

Given there were no significant effects of RCT treatment group on the immediate response to a single-session of LVR, change in respiratory function pre and post the LVR therapy session conducted at the final assessment (Timepoint 3) was summarised for the cohort as a whole. Table 8-16 represents the immediate effect of LVR observed in this population of participants with heterogeneous NMD and prior exposure to the testing procedure (in contrast to Table 7-3, which presents this information when participants were naïve to LVR). There were statistically significant decreases in FRC (p=0.029), TLC (p=0.049) and PCF (p=0.001) at Timepoint 3b compared to 3a, but no change in the primary or secondary outcomes of interest (LIC, C_{rs}, specific C_{rs}, VC).

Variable	n	Timepoint 3a mean±SD	Timepoint 3b mean±SD	Δ at Time 3 Mean difference (95% CI)	*p*-value
LIC (L)	66	1.99 ± 0.98	1.98 ± 0.96	-0.01 (-0.07, 0.05)	0.690
VC (L)	66	1.44 ± 0.83	1.44 ± 0.82	-0.01 (-0.04, 0.03)	0.728
LIC-VC (L)	66	0.55 ± 0.44	0.54 ± 0.45	-0.01 (-0.07, 0.05)	0.810
C_{rs} (L/cmH_2O)	60	0.0412 ± 0.0272	0.0420 ± 0.0281	0.0008 (-0.0014, 0.0030)	0.472
Specific C_{rs}	46	0.0426 ± 0.0359	0.0430 ± 0.0381	0.0003 (-0.0028, 0.0035)	0.825
FRC (L)	48	1.33 ± 1.06	1.29 ± 1.00	-0.05 (-0.09, -0.01)	**0.029**
TLC (L)	48	2.49 ± 1.41	2.44 ± 1.39	-0.04 (-0.09, 0.00)	**0.049**
RV (L)	48	1.00 ± 0.82	0.97 ± 0.78	-0.03 (-0.06, 0.01)	0.096
ERV (L)	48	0.33 ± 0.32	0.31 ± 0.30	-0.02 (-0.05, 0.01)	0.154
IC (L)	48	1.15 ± 0.63	1.16 ± 0.62	0.01 (-0.02, 0.05)	0.410
PCF (L/min)	66	165.2 ± 58.1	156.1 ± 60.1	-9.2 (-14.6, -3.7)	**0.001**
PCF_{LIC} (L/min)	65	186.3 ± 57.8	183.5 ± 52.7	-2.8 (-9.6, 4.0)	0.417
PCF_{LIC} – PCF	65	21.2 ± 36.8	27.3 ± 38.6	6.1 (-1.6, 13.8)	0.120

Table 8-16: Summary data of the immediate effect of LVR on respiratory function, at Timepoint 3

Total number of participants who completed assessments at Timepoint 3 = 73. Δ at Time 3 = Timepoint 3b minus 3a.
(n) = the number of participants with technically acceptable measurements at both timepoints. Results were not obtainable in all due to bulbar impairment, technical issues or fatigue. *P*-value represents paired t-test comparison (Timepoint 3b minus 3a); data in **bold** indicate statistically significant values ($p<0.05$). **Contrast with** Table 7-3**, which presents this information when participants were naïve to LVR.**
LIC = lung insufflation capacity, VC = vital capacity, LIC – VC = LIC minus VC difference, C_{rs} = Total respiratory system compliance, Specific C_{rs} = C_{rs} divided by FRC, FRC = Functional residual capacity, TLC = Total lung capacity, RV = Residual volume, ERV = Expiratory reserve volume, IC = Inspiratory capacity, PCF = Peak cough flow, PCF_{LIC} = PCF from LIC, PCF_{LIC} –PCF = PCF_{LIC} minus PCF difference.

8.13 RESULTS: COMPARISON BETWEEN IMMEDIATE EFFECTS AT BASELINE AND FINAL ASSESSMENT

The immediate physiological effects of a single-session of LVR in a naïve population (Δ at Timepoint 0) were compared to the change in the same cohort after three-months (Δ at Timepoint 3). Linear mixed models comparing the effect of time (Δ at Time 0 *vs.* Δ at Time 3) with disease type (MND *vs.* Other NMD) and RCT treatment (LVR *vs.* active control) included as factors are presented in Table 8-17.

Models for C_{rs}, LIC – VC, PCF_{LIC} and FRC were significant overall (Table 8-17). The effect of a single-session of LVR on C_{rs} was different over time for participants with MND, in that the immediate improvement in C_{rs} when naïve was not evident at the final assessment (Figure 8-20).

Similar findings were identified for the LIC – VC difference and PCF_{LIC}; the improvements in LIC – VC and PCF_{LIC} following the single-session at Time 0 were not observed at Time 3 (Figures in Appendix 11.5.8; Table 8-18). Whilst the model examining the effect on LIC was not significant overall, a main effect of time was identified (Table 8-17, Figure 8-21). Post-hoc analysis suggested that the immediate improvement observed in LIC at Timepoint 0 when participants were naïve was not seen at study conclusion (Table 8-18).

Disease effects were statistically significant in the FRC model, and indicated that FRC fell in participants with MND compared to Other NMDs over the pre-post intervention sessions. A Treatment effect was also found and signified a between-group difference at baseline (Figure in Appendix 11.5.8).

No significant effect of Treatment by Time was found for any of the respiratory variables, confirming that regular LVR did not alter the immediate response to a single-session of therapy.

Variable model	χ^2	*p*-value
Delta LIC model: log restricted likelihood = -45.0	*13.4*	*0.063*
Treatment	1.78	0.182
Time	9.22	**0.002**
Treatment*Time	1.00	0.318
Disease	0.79	0.375
Treatment*Disease	0.47	0.491
Time*Disease	1.95	0.162
Treatment*Time*Disease	0.13	0.718
Delta VC model = 60.1	*7.3*	*0.401*
Treatment	0.27	0.602
Time	1.63	0.201
Treatment*Time	2.65	0.104
Disease	0.25	0.617
Treatment*Disease	1.04	0.309
Time*Disease	2.00	0.157
Treatment*Time*Disease	0.85	0.356
Delta LIC – VC model = -44.2	***16.0***	***0.025***
Treatment	1.10	0.295
Time	12.78	**0.0003**
Treatment*Time	0.12	0.729
Disease	0.90	0.344
Treatment*Disease	0.04	0.849
Time*Disease	3.58	0.059
Treatment*Time*Disease	0.65	0.419
Delta C_{rs} model = 338.0	***17.1***	***0.017***
Treatment	0.18	0.670
Time	5.69	**0.017**
Treatment*Time	0.08	0.778
Disease	8.32	**0.004**
Treatment*Disease	0.00	0.970
Time*Disease	3.80	0.051
Treatment*Time*Disease	0.38	0.536
Delta Specific C_{rs} model = 248.1	*7.3*	*0.395*
Treatment	0.57	0.449
Time	0.49	0.482
Treatment*Time	0.00	0.978

Variable model		χ^2	*p*-value
	Disease	0.41	0.524
	Treatment*Disease	0.11	0.742
	Time*Disease	1.88	0.171
	Treatment*Time*Disease	0.22	0.637
Delta FRC model = 21.8		***19.5***	***0.007***
	Treatment	4.61	**0.032**
	Time	1.20	0.274
	Treatment*Time	1.15	0.284
	Disease	11.54	**0.0007**
	Treatment*Disease	0.61	0.436
	Time*Disease	0.60	0.437
	Treatment*Time*Disease	0.00	0.984
Delta TLC model = 24.2		*7.3*	*0.400*
	Treatment	0.86	0.354
	Time	0.09	0.759
	Treatment*Time	0.06	0.807
	Disease	5.64	**0.018**
	Treatment*Disease	0.08	0.784
	Time*Disease	0.03	0.862
	Treatment*Time*Disease	0.01	0.937
Delta RV model = 24.6		*7.3*	*0.397*
	Treatment	0.57	0.452
	Time	0.07	0.795
	Treatment*Time	0.00	0.947
	Disease	4.21	**0.040**
	Treatment*Disease	0.13	0.719
	Time*Disease	1.08	0.298
	Treatment*Time*Disease	0.33	0.565
Delta PCF model = -669.7		*6.2*	*0.514*
	Treatment	0.35	0.554
	Time	0.64	0.425
	Treatment*Time	0.02	0.878
	Disease	1.61	0.205
	Treatment*Disease	0.24	0.627
	Time*Disease	1.46	0.228
	Treatment*Time*Disease	1.35	0.246

Variable model	χ^2	*p*-value
Delta PCF_{LIC} model = -651.1	***16.9***	***0.018***
Treatment	2.34	0.126
Time	6.08	**0.014**
Treatment*Time	1.29	0.256
Disease	0.93	0.334
Treatment*Disease	2.19	0.139
Time*Disease	0.48	0.487
Treatment*Time*Disease	0.62	0.431
Delta PCF_{LIC} – PCF model = -701.9	*13.1*	*0.070*
Treatment	2.87	0.090
Time	1.50	0.221
Treatment*Time	0.24	0.623
Disease	3.02	0.082
Treatment*Disease	2.58	0.108
Time*Disease	1.48	0.223
Treatment*Time*Disease	0.00	0.996

Table 8-17: Linear mixed models of effect of i) Time, Disease and Treatment on the immediate change in respiratory function following a single-session of LVR (Delta variable)

Time represents baseline (Time 0) and final (Time 3) assessments, Disease represents MND or Other NMD, and Treatment indicates participants randomised to regular LVR or Active Control for the three-month RCT period.

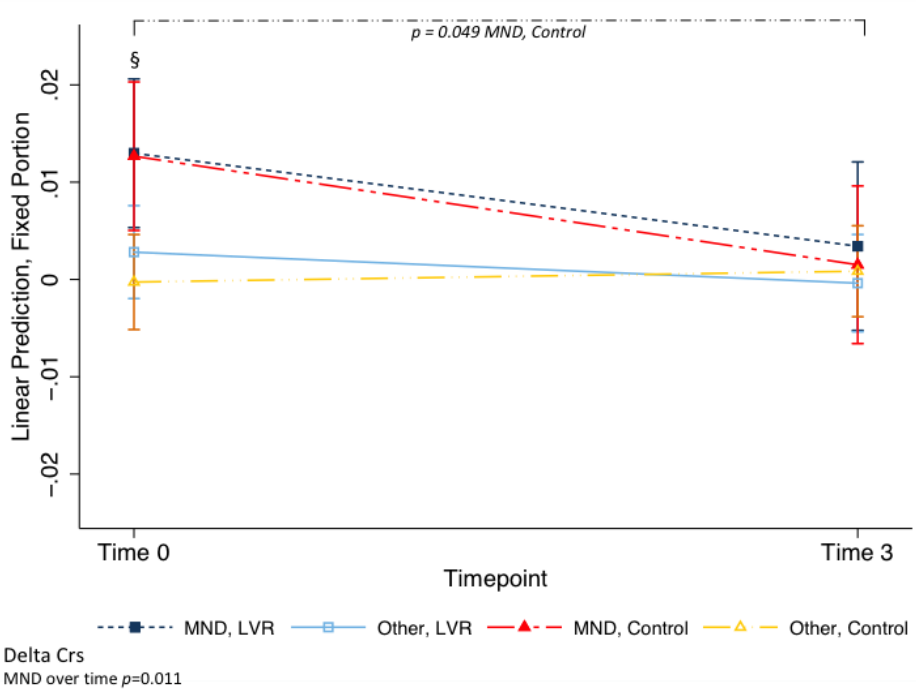

Figure 8-20: Linear mixed model – effects of time on the immediate C_{rs} response, by disease type and treatment

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of time on the immediate respiratory system compliance response (change in C_{rs} post- minus pre- a single-session of LVR, Delta C_{rs}), by disease type and treatment. ***Model significant and main effects of time and disease present.*** *P*-values refer to statistically significant comparisons between the estimated margins, where § represents differences between disease type (MND vs Other NMDs, $p<0.0001$ at Time 0), and line pattern represents statistically significant differences over time ("MND, Control"). MND over time also significant (Time 3 vs 0 $p=0.011$).

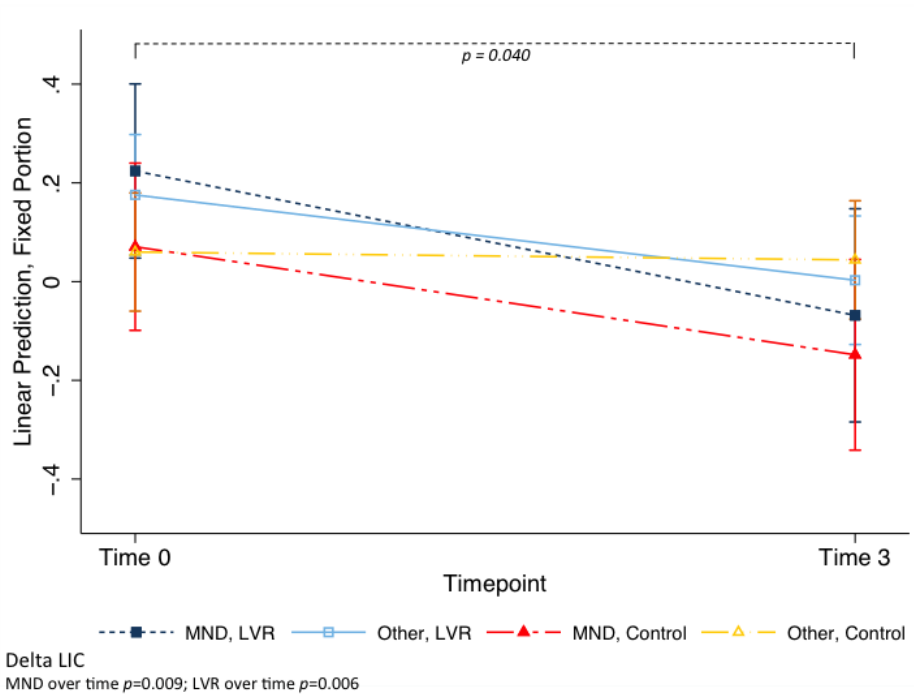

Figure 8-21: Linear mixed model – effects of time on the immediate LIC response, by disease type and treatment

Linear mixed model illustrating the estimated mean (95% CI) marginal effects of time on the immediate lung insufflation capacity response (change in LIC post- minus pre- a single-session of LVR, Delta LIC), by disease type and treatment. ***Model not significant however main effect of time present.*** *P*-value refers to statistically significant comparisons between the estimated margins, where line pattern represents statistically significant difference over time ("MND, LVR"). MND over time (Time 3 vs 0 p=0.009) and LVR over time also significant (Time 3 vs 0 p=0.006).

Variable	Δ at Time 0 Mean difference (95% CI)	n_{T0}	Δ at Time 3 Mean difference (95% CI)	n_{T3}	Mean difference (95% CI) (Δ T3 minus Δ T0)	n	*p*-value
LIC (L)	0.13 (0.04, 0.21)**	76	-0.01 (-0.07, 0.05)	66	-0.11 (-0.21, -0.02)	66	**0.022**
VC (L)	-0.02 (-0.06, 0.02)	76	-0.01 (-0.04, 0.03)	66	0.02 (-0.02, 0.07)	66	0.252
LIC-VC (L)	0.15 (0.06, 0.23)**	76	-0.01 (-0.07, 0.05)	66	-0.14 (-0.23, -0.04)	66	**0.005**
C_{rs} (L/cmH_2O)	0.0046 (0.0009, 0.0083)**	63	0.0008 (-0.0014, 0.0030)	60	-0.0022 (-0.0068, 0.0023)	54	0.331
Specific C_{rs}	0.0042 (0.0013, 0.0072)**	43	0.0003 (-0.0028, 0.0035)	46	-0.0045 (-0.0087, -0.0004)	37	**0.031**
PCF (L/min)	-7.1 (-16.5, 2.4)	76	-9.2 (-14.6, -3.7)**	66	-0.8 (-10.4, 8.9)	66	0.874
PCF_{LIC} (L/min)	12.3 (4.5, 20.2)**	75	-2.8 (-9.6, 4.0)	65	-14.1 (-25.9, -2.3)	64	**0.020**
PCF_{LIC} – PCF	19.5 (6.6, 32.3)**	75	6.1 (-1.6, 13.8)	65	-13.6 (-29.8, 2.7)	64	0.101

Table 8-18: Comparison between the immediate effect of LVR at study commencement (Timepoint 0) and conclusion (Timepoint 3), for selected respiratory function variables.

Δ at Time 0 = Time 0b minus 0a, n_{T0} = number of randomised participants with paired data at Time 0; Δ at Time 3 = Time 3b minus 3a, n_{T3} = number of participants with paired data at Time 3

(n) = the number of participants with technically acceptable measurements at all four timepoints. Results were not obtainable in all due to bulbar impairment, technical issues or fatigue. *P*-value represents paired t-test between timepoints (**bold** indicates statistically significant difference $p<0.05$) and "**" indicates statistically significant difference on paired t-test within the stated timepoint (e.g., Time 0b minus T0a, $p<0.05$).

LIC = lung insufflation capacity, VC = vital capacity, LIC – VC = LIC minus VC difference, C_{rs} = Total respiratory system compliance, Specific C_{rs} = C_{rs} divided by FRC, PCF = Peak cough flow, PCF_{LIC} = PCF from LIC, PCF_{LIC}–PCF = PCF_{LIC} minus PCF difference.

8.14 RESULTS: EXPLORATORY ANALYSES – POTENTIAL MECHANISM OF CHANGE

Given the significant effect of LVR on the primary outcome of LIC and the LIC – VC difference, and the within-treatment group increase over three months in PCF_{LIC} and the PCF_{LIC} – PCF difference, additional exploratory analyses were conducted. Firstly, analyses were performed to test the hypothesis that improvements in LIC were driving the increases observed in LIC – VC, PCF_{LIC} and PCF_{LIC} – PCF, given they are performed or derived from LIC. Change in LIC was very strongly associated with the improvement in the LIC – VC difference over the study, in all treatment and disease type sub-groups (Table 8-19; Figure 8-22).

	Δ LIC				**Δ PCF_{LIC} – PCF**			
r p-value	**LVR**		**Control**		**LVR**		**Control**	
Δ LIC – VC								
All	0.83	**<0.0001**	0.86	**<0.0001**	-0.12	0.513	0.20	0.224
MND	0.94	**<0.0001**	0.88	**0.0001**	-0.26	0.466	0.34	0.252
Other	0.83	**<0.0001**	0.92	**<0.0001**	-0.21	0.328	0.11	0.579
Δ PCF_{LIC}								
All	0.06	0.736	0.31	0.058	0.80	**<0.0001**	0.48	**0.002**
MND	0.07	0.829	0.17	0.573	0.32	0.360	0.67	**0.012**
Other	-0.02	0.913	0.35	0.079	0.86	**<0.0001**	0.38	0.058

Table 8-19: Correlation between change in LIC over 3-months and change in variables derived or performed from LIC.

Data represent Pearson's r correlation coefficient and *p*-value, for change in the stated variables over the three-month study period (Timepoint 3a minus 0a). **Bold** *p*-values refer to comparisons that were statistically significant ($p<0.05$). The number of participants with paired data = LVR (33), Control (39).

All = heterogeneous neuromuscular disease; MND = motor neurone disease sub-group; Other = other neuromuscular diseases including chest wall disease sub-group.

LIC = lung insufflation capacity (litres), PCF_{LIC} = peak cough flow from LIC (litres per minute), PCF_{LIC} – PCF = peak cough flow from LIC minus peak cough flow difference (L/min), LIC – VC = lung insufflation capacity minus vital capacity difference (L).

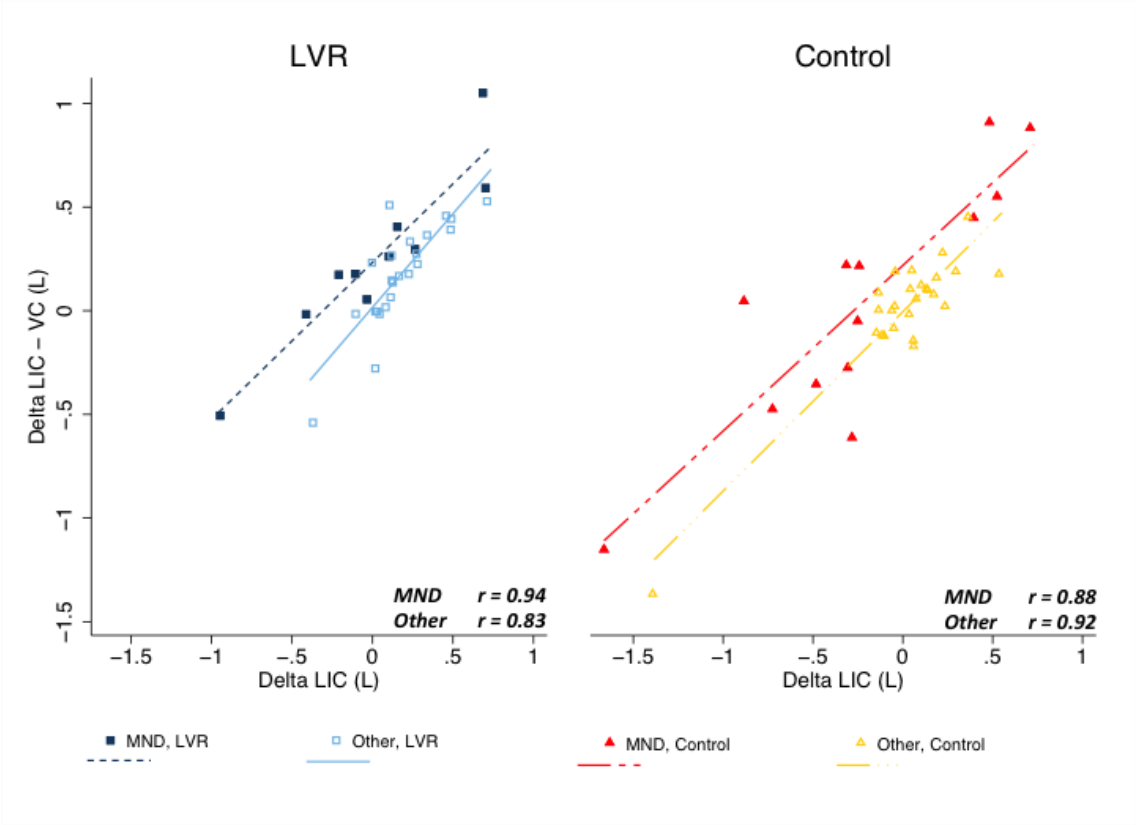

Figure 8-22: Relationship between change in LIC and change in LIC – VC difference, by treatment

Markers represent individual participant change over time values (delta = Timepoint 3a minus 0a); line represents the line of best fit.
LIC = lung insufflation capacity (litres); LIC – VC = lung insufflation capacity minus vital capacity difference (litres); LVR = lung volume recruitment group; Control = active control group; MND = motor neurone disease; Other = other neuromuscular diseases including chest wall disease. Pearson's r refers to the MND and Other sub-groups, by treatment (statistically significant values in **bold**).

No relationship was found between changes in PCF_{LIC} and LIC over time (Table 8-19) however the absolute values of PCF_{LIC} and LIC were related at baseline as well as the final study visit (both timepoints r=0.55, p<0.0001; Figures in Appendix 11.5.9).

The improvement in the PCF_{LIC} – PCF difference over the three-months was associated with the change in PCF_{LIC}; greater increase in PCF_{LIC} was related to a larger PCF_{LIC} – PCF difference, particularly in participants in the Other NMD, LVR sub-group (Table 8-19; Figure 8-23). In contrast, improvement in the LIC – VC difference was not related to an improvement in the PCF_{LIC} – PCF difference (Table 8-19; Figure in Appendix 11.5.9).

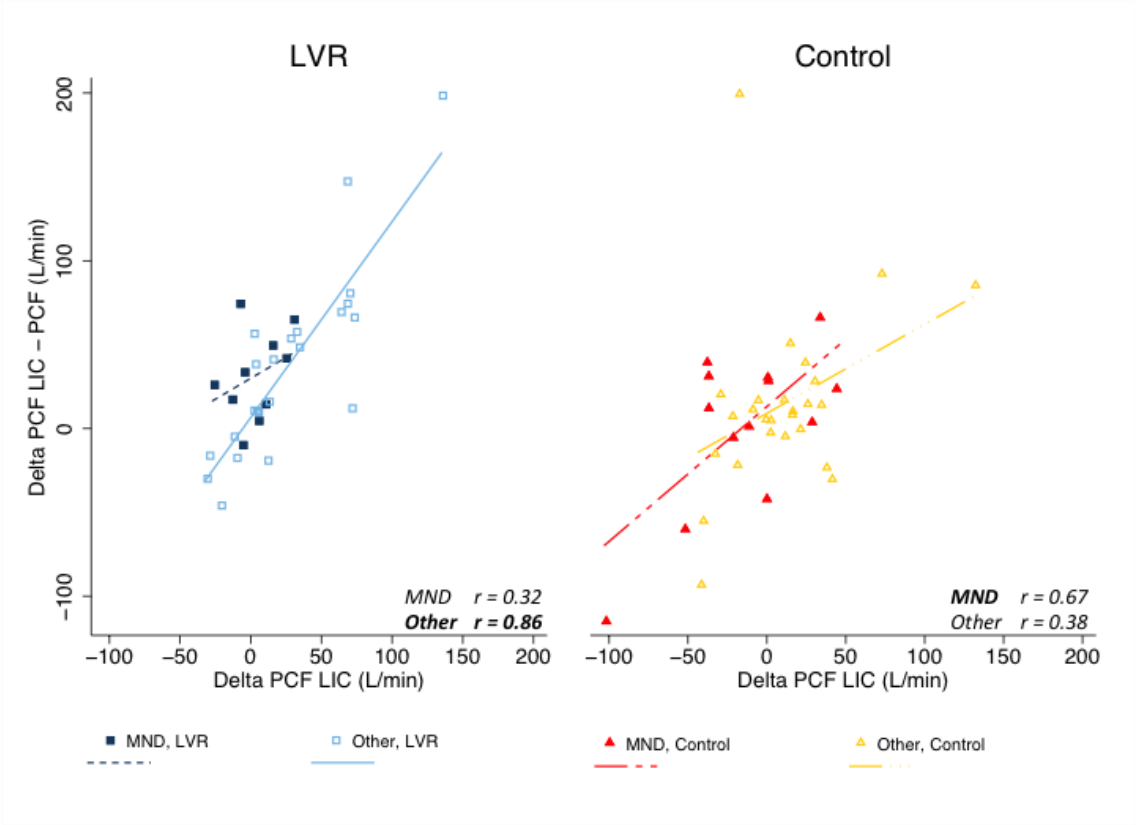

Figure 8-23: Relationship between change in PCF_{LIC} and change in PCF_{LIC} – PCF difference, by treatment

Markers represent individual participant change over time values (delta = Timepoint 3a minus 0a); lines represent the line of best fit.
PCF_{LIC} = peak cough flow from lung insufflation capacity; PCF_{LIC} – PCF = PCF_{LIC} minus unassisted peak cough flow difference (litres per minute); LVR = lung volume recruitment group; Control = active control group; MND = motor neurone disease; Other = other neuromuscular diseases including chest wall disease. Pearson's r refers to the MND and Other sub-groups, by treatment (statistically significant values in **bold**).

Next, the relationship between change in LIC and change in respiratory function was considered. Outcome measures were selected based on respiratory physiology "first-principles", with the hypothesis that the improvement in LIC observed may be related to an improvement in lung volume (VC, FRC or TLC) and/or C_{rs}.

There was a moderate relationship between the change in LIC and VC across the three-month study period in the LVR (r=0.45, *p*=0.009) and Control arms (r=0.46, *p*=0.003) (Table 8-20, Figure 8-24). No associations were found between changes in LIC and FRC, TLC, C_{rs} or specific C_{rs} on univariate analysis (Figures in Appendix 11.5.9).

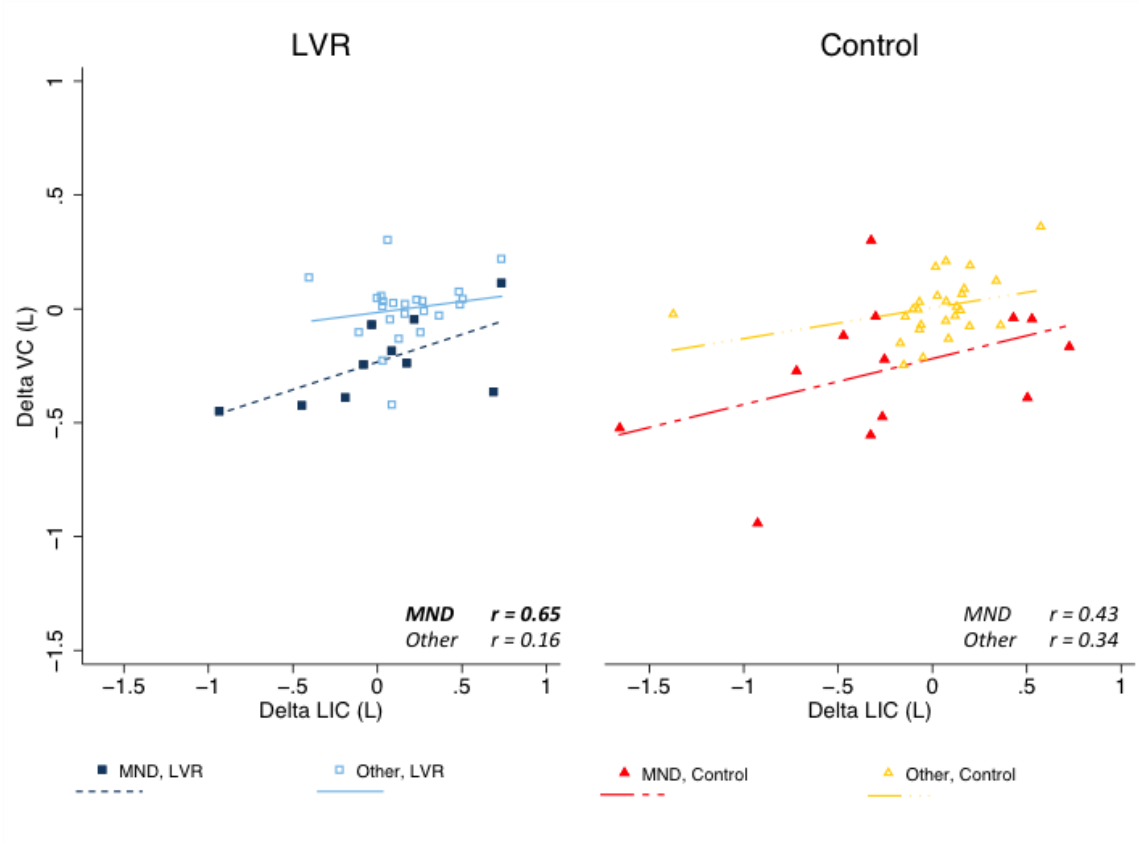

Figure 8-24: Relationship between change in LIC and change in VC, by treatment

Markers represent individual participant change over time values (delta = Timepoint 3a minus 0a); lines represent the line of best fit. LIC = lung insufflation capacity (litres); VC = vital capacity (litres); LVR = lung volume recruitment group; Control = active control group; MND = motor neurone disease; Other = other neuromuscular diseases including chest wall disease. Pearson's r refers to the MND and Other sub-groups, by treatment (statistically significant values in **bold**).

Correlation with Δ LIC	LVR			Control		
	n	Pearson's r	p-value	n	Pearson's r	p-value
Δ VC						
All	34	0.45	**0.009**	39	0.46	**0.003**
MND	10	0.65	**0.043**	13	0.43	0.145
Other	24	0.16	0.470	26	0.34	0.093
Δ FRC						
All	26	0.16	0.436	30	-0.22	0.253
MND	6	0.53	0.274	8	-0.25	0.554
Other	20	0.01	0.982	22	-0.13	0.572
Δ TLC						
All	26	0.26	0.206	30	0.07	0.699
MND	6	0.57	0.239	8	0.00	0.995
Other	20	0.07	0.765	22	-0.13	0.573
Δ C_{rs}						
All	30	-0.22	0.242	32	0.29	0.102
MND	8	-0.44	0.278	10	0.63	0.053
Other	22	0.22	0.335	22	-0.48	0.024
Δ Specific C_{rs}						
All	25	-0.11	0.589	26	0.22	0.282
MND	6	0.03	0.948	6	0.80	0.056
Other	19	-0.16	0.507	20	0.07	0.765

Table 8-20: Correlation between change in LIC over 3-months and respiratory function

Data represent correlations between changes in lung insufflation capacity (litres) and the stated variables over the three-month study period (Timepoint 3a minus 0a).

(n) = number of participants with paired data, Pearson's r = Pearson's correlation coefficient. *P*-values <0.05 considered statistically significant (in **bold**).

All = heterogeneous neuromuscular disease; MND = motor neurone disease sub-group; Other = other neuromuscular diseases including chest wall disease sub-group. VC = vital capacity, FRC = functional residual capacity, TLC = total lung capacity (all measured in litres); C_{rs} = total respiratory system compliance (L/cmH_2O); Specific C_{rs} = specific respiratory system compliance ($L/cmH_2O/L$).

The relationship between LIC and the peak inspiratory pressure achieved during measurement of LIC was considered. The peak pressure was similar between the LVR and Control arms at Timepoint 0a (mean difference = -1.3 (-5.2, 2.7) cmH_2O, p=0.533) and Timepoint 3a (mean difference = 0.2 (-4.7, 5.1) cmH_2O, p=0.936) (Table 8-21). Furthermore, the pressure corresponding to the recorded LIC value did not increase significantly over the three-months within the LVR (p=0.098) or Control (p=0.374) groups. However, participants with Other NMDs did insufflate to a statistically higher pressure at the final assessment compared to baseline, regardless of treatment (Table 8-21).

Moreover, there was a statistically significant association between the change in peak pressure at LIC over the study duration, and change observed in LIC. Participants in the LVR arm demonstrated a moderate association (r=0.55, p=0.001), whereas no significant relationship was identified in the Control group (r=0.20, p=0.234) (Figure 8-25).

	Pressure at LIC Time 0a		Pressure at LIC Time 3a		Change in pressure (Pressure T3a – T0a)	*p*-value
LVR	31.6 ± 7.6	(37)	34.7 ± 12.1	(32)	3.5 (-0.7 – 7.7)	0.098
LVR, MND	31.4 ± 6.0	(12)	29.7 ± 7.6	(10)	-2.0 (-9.7 – 5.7)	0.565
LVR, Other	31.6 ± 8.4	(25)	37.0 ± 13.2	(22)	6.0 (1.0 – 11.1)	**0.021**
Control	32.8 ± 9.6	(39)	34.5 ± 8.7	(39)	1.7 (-2.2 – 5.6)	0.374
Control, MND	34.3 ± 13.1	(13)	31.9 ± 9.4	(13)	-2.4 (-12.3 – 7.4)	0.601
Control, Other	32.1 ± 7.6	(26)	35.9 ± 8.2	(26)	3.8 (0.2 – 7.4)	**0.038**

Table 8-21: Measured peak inspiratory pressure recorded at LIC, at Timepoints 0a and 3a

Data are presented as mean ± standard deviation and mean difference (95% confidence interval). Pressure measured in centimetres of water (cmH_2O). **Bold** p-values refer to comparisons that were statistically significant (p<0.05).
(n) = number of participants. LIC = lung insufflation capacity, LVR = lung volume recruitment group; Control = active control group; MND = motor neurone disease; Other = other neuromuscular diseases including chest wall disease.

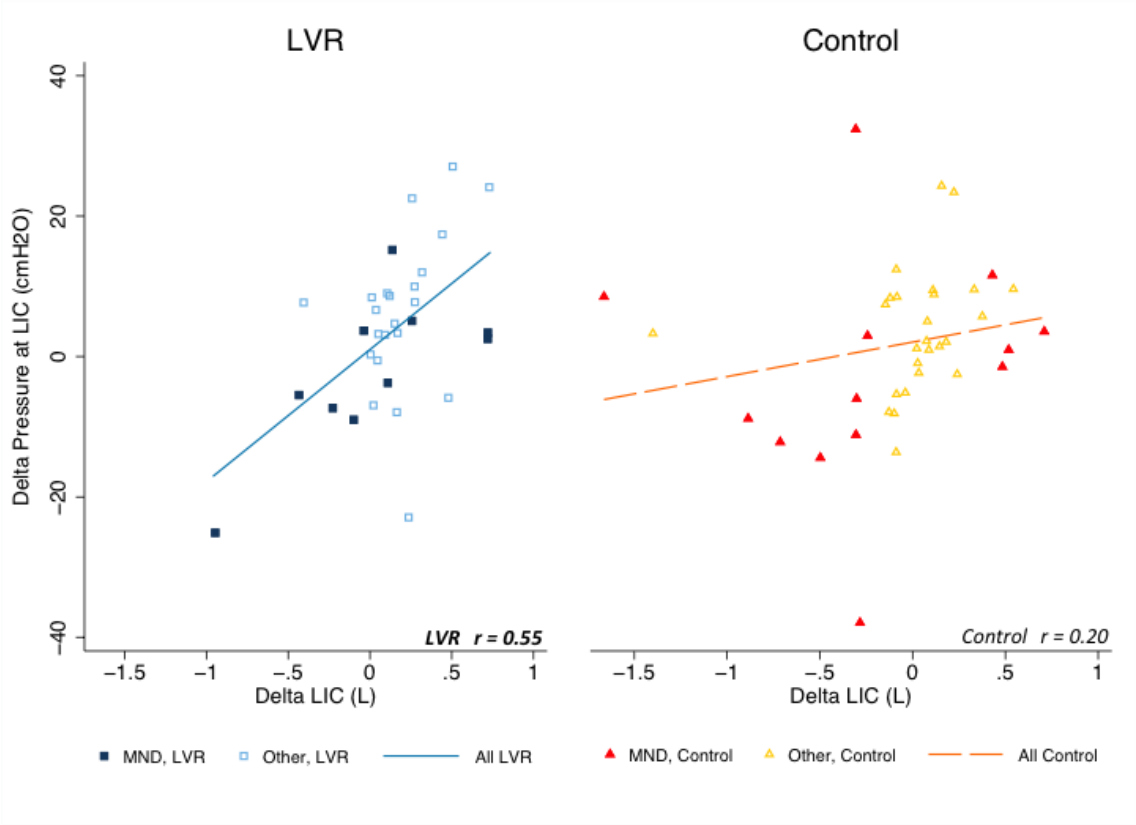

Figure 8-25: Relationship between change in LIC and change in pressure at LIC, by treatment

Markers represent individual participant change over time values (delta = Timepoint 3a minus 0a); lines represent the line of best fit.
LIC = lung insufflation capacity (litres); Pressure at LIC = measured pressure at LIC (centimetres of water); LVR = lung volume recruitment group; Control = active control group; MND = motor neurone disease; Other = other neuromuscular diseases including chest wall disease. Pearson's r refers to the LVR and Control groups (statistically significant values in **bold**).

Finally, the results of Section 8.13 suggested LIC increased following a single-session of LVR in naïve participants but not at study conclusion (Table 8-17, Figure 8-21), potentially indicating skill acquisition. Post-hoc analyses were therefore conducted using Timepoint 0a to represent a "naïve user's baseline", and repeated using Timpeoint 0b (i.e., following a short standardised LVR session) to explore the influence of a learning effect (Table 8-22).

	0a to 0b		0a to 1		0a to 2		0a to 3a		0a to 3b	
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**	**LVR**	**Control**	**LVR**	**Control**
Mean change **LIC 95% CI (n)**	0.19 0.07, 0.31 (37)	0.06 -0.05, 0.18 (39)	0.18 0.05, 0.31 (35)	-0.14 -0.27, - 0.02 (38)	0.13 0.01, 0.25 (35)	-0.11 -0.25, 0.04 (39)	0.13 0.01, 0.24 (33)	-0.07 -0.22, 0.09 (39)	0.14 0.02, 0.26 (30)	-0.05 -0.19, 0.10 (36)
***p*-value**	***0.002***	*0.261*	***0.007***	***0.030***	***0.032***	*0.137*	***0.039***	*0.380*	***0.022***	*0.506*

	0b to 1		0b to 2		0b to 3a		0b to 3b	
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**	**LVR**	**Control**
	-0.01 -0.13, 0.11 (35)	-0.20 -0.32, - 0.09 (38)	-0.07 -0.19, 0.05 (35)	-0.17 -0.29, - 0.05 (39)	-0.05 -0.20, 0.10 (33)	-0.13 -0.27, 0.01 (39)	-0.04 -0.20, 0.12 (30)	-0.08 -0.21, 0.05 (36)
	0.822	***0.001***	*0.249*	***0.007***	*0.509*	*0.060*	*0.636*	*0.208*

	1 to 2		2 to 3a		3a to 3b	
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**
	-0.04 -0.12, 0.04 (34)	0.05 -0.04, 0.15 (38)	-0.03 -0.14, 0.07 (32)	0.04 -0.07, 0.15 (39)	-0.02 -0.12, 0.08 (30)	-0.01 -0.09, 0.07 (36)
	0.345	*0.251*	*0.523*	*0.467*	*0.741*	*0.820*

Table 8-22: Post-hoc pairwise comparisons of change in LIC over time, by treatment group

Data are presented as mean change in lung insufflation capacity (LIC, L) (95% confidence interval). **Bold** *p*-values refer to comparisons that were statistically significant ($p<0.05$) on Student's paired *t*-test.
(n) = number of participants with paired data. LVR = lung volume recruitment group; Control = active control group. 0a = Timepoint 0a (Baseline pre-LVR), 0b = Timepoint 0b (Baseline post-LVR), 1 = Timepoint 1 (1-month post randomisation), 2 = Timepoint 2 (2-months post randomisation), 3a = Timepoint 3a (Final pre-LVR), 3b = Timepoint 3b (Final post-LVR).

9 DISCUSSION

The primary objective of this thesis was to determine the effect of regular LVR on respiratory function, symptoms and HRQoL in participants with NMD. This work suggests that LVR increases LIC and the "recruitable volume" (i.e., LIC – VC difference) when prescribed twice a day for three-months. No difference in VC, static lung volumes, respiratory system compliance, symptoms or HRQoL was observed between the treatment groups. We found no relationship between improvement in LIC and lung volumes or $C_{rs,}$ and no evidence of a dose-response, despite employing an objective measure of LVR use and diary self-report. We speculate that over a three-month period, regular LVR may produce a *practice* effect as opposed to a *treatment* effect, in that participants tolerate or acclimatise to higher assisted inflation pressures, thereby achieving a larger LIC and LIC – VC difference. Moreover, the improvement in LIC observed in participants in the intervention group may represent a larger *learning* effect prior to randomisation (from Time 0a to Time 0b), purely by chance.

Secondary findings of this research project suggest that respiratory function is different between participants with MND and Other NMDs; although this cohort as a whole had severe reduction in vital capacity and ventilatory restriction, this was associated predominantly with respiratory muscle weakness in MND, whereas more slowly-progressive conditions were characterised by weakness *and* stiffness of the respiratory system. This finding supports the long-held view that reduced respiratory system compliance compounds respiratory dysfunction in people with NMD, producing greater lung volume loss for similar impairment of respiratory muscle strength.

Furthermore, participants with Other NMDs were 3.5 times more likely to have experienced a RTI in the previous year. Whilst RTI was associated with lower lung volumes and PCF, these measures were not sensitive in differentiating those participants who reported a prior RTI episode. Although 90% of the study cohort had a PCF below the minimum threshold believed necessary to prevent hospital admissions and reduce the risk of pneumonia (<270 L/min),[194] only 43% of participants reported an acute episode in the year prior. Cut-offs of VC <1.1 L or PCF <160 L/min yielded 60-

64% sensitivity and 50-54% specificity for identifying participants with a past history of RTI, again suggesting that the relationship between RTI and a single respiratory function measure is indiscriminate.

This work has also demonstrated that LVR is a simple technique to learn; 76% of participants achieved a LIC at least 10% greater than their VC within the first attempt, with this figure increasing to 95% after a short training session. A single-session of LVR was shown to improve C_{rs}, LIC, the LIC – VC difference, PCF_{LIC} and the PCF_{LIC} – PCF difference, however this response was only noted when participants were naïve to the technique. Respiratory function did not change following a single-session of LVR when participants were familiar with the technique via monthly LIC assessments, implying that there is an initial *learning* or "skill acquisition" effect. Moreover, no single-session change was seen in participants who performed twice-daily LVR for three-months, suggesting that regular LVR does not enhance immediate respiratory effects of a single therapy session when participants are medically-stable. Whether regular LVR has a carry-over effect to the immediate response to assisted inflation therapy when it is performed during an acute respiratory episode remains to be determined.

9.1 DISCUSSION OF RCT FINDINGS

In the RCT examining the physiological effects of LVR prescribed twice-daily for a three-month period in participants with NMD, the primary outcome LIC increased in the intervention arm and remained stable in the active control group. There was a statistically significant treatment by time interaction, with post-hoc between-group comparison indicating a statistically significant difference after two months, but not at the three-month timepoint (mean difference = 190 mL (0 to 390 mL), p=0.054). Vital capacity declined in both groups over time. Consequentially, the improvement in the LIC – VC difference was greater in the LVR group. Although C_{rs} and specific C_{rs} improved in the LVR arm, there were no significant between-group differences. No changes were observed in static lung volumes or respiratory muscle strength. Peak cough flow declined over the three months in the intervention group, however PCF_{LIC}

increased. The PCF_{LIC} – PCF difference improved in the LVR group but remained unchanged in the active control arm.

Our finding of a significant treatment by time interaction provides sound evidence that regular LVR can improve LIC in people with progressive NMDs. The significant mean increase in LIC of 130 (10 to 240) mL in the LVR group after three-months (n=33) is consistent with the 154 mL (-13 to 322 mL, *p*=0.07) change observed in a prospective uncontrolled three-month feasibility study.[220] The cohort of 16 completed participants had similar diagnoses (MND, PPS or myotonic dystrophy) but milder respiratory impairment than our controlled study. In contrast, Marques and colleagues observed no change in the MIC (analogous to LIC) of young adults with SMA or muscular dystrophies, who were prescribed LVR daily and followed for 4-6 months. Their population were not on ventilation and had better preserved lung function (mean FVC = 1.78 ± 0.60 L),[213] whereas the comparable sub-group of people with similar diagnoses in this study (Other NMD) had a mean VC of 1.30 ± 0.77 L (35 ± 17% predicted normal). This could suggest that there is an amount of lung volume loss below which such therapies may be efficacious, and that there is little demonstrable effect if commenced too early in the disease process.

Retrospective cohort studies have similarly observed improvement in LIC or MIC when LVR has been practised regularly for more than one-year.[136,137] In a cohort of 22 patients with DMD, an increase of 100 ± 400 mL following initiation of LVR therapy was observed alongside a concomitant deceleration in the rate of FVC decline (median follow-up 45 months).[137] Larger increases have been described by Bach, Kang and colleagues. A mean increase in MIC or LIC of 246 mL was observed in 47 patients with DMD,[216] with improvements of 365 ± 289 mL (n=46)[209] and 307 ± 297 mL (n=30)[208] reported in heterogeneous NMD case series. Methodological limitations may explain some of the discrepancy in the magnitude of effect between previous literature and the current RCT; these cohort studies rely on self-report of performing regular LVR, reflect patients who returned for multiple visits, often with considerable drop-out,[209] [208] and in one case, exclude data from those who did not improve.[208]

The shorter duration of the current study is another factor very likely to be influencing effect size. Our findings show that LVR has a demonstrable effect on LIC over three months, consistent with an uncontrolled study of the same length.[220] Although not all the retrospective case studies clearly state the follow-up period,[209] [208] it is plausible that a longer intervention period is required to demonstrate greater improvement, especially in participants with long-standing and/or slowly-progressive NMD.

Contrary to the improvement in LIC, we found LVR had no beneficial effect on VC. Vital capacity fell over three months, with no difference in the model between the LVR or Control groups. This decline was attributable to participants with MND; VC remained stable in the Other NMD sub-group, regardless of treatment. Our results are comparable to the two prospective, uncontrolled studies of less than six months duration, in which VC did not change[213] or decreased,[220] but contrast with observations from longer-duration cohorts. As in the present study, the small decline in FVC seen over the three-month study by Kaminska and colleagues was also largely attributable to participants with MND.[220]

Longer longitudinal studies of participants with DMD have suggested that LVR slows the decline in VC,[136,137] or that LIC increases in the face of falling VC[209,220] resulting in a concomitant improvement in the LIC – VC difference. In the study by Katz and colleagues that followed 16 participants with DMD for a median of 6.1 years, the rate of decline of FVC %predicted per year fell from 4.5% prior to LVR initiation, to 0.5% once LVR was commenced.[136] However at the time LVR was started, median age was 19.3 years, median FVC was already severely low at 14% predicted and 94% of the cohort used domiciliary NIV. This slowing of lung volume decline could therefore in part be attributable to natural disease progression.

Observations from a cohort study, reporting on 43 patients with MND and slowly-progressive NMDs, similarly suggested an effect of LVR on VC. In the sub-group of 30 participants prescribed LVR in whom MIC increased over time, VC increased and PCF remained stable. In contrast, VC and PCF fell in the 13 participants who reported a declining MIC over the follow-up period.[208] However these associations between changes in LIC and VC should be interpreted with some caution given the limitations

inherent with a cohort design. Although our data also indicate that increasing LIC values are moderately associated with improvement in VC (see Table 8-20 and Figure 8-24), this was demonstrated in *both* the LVR (r=0.45) and control groups (r=0.46). These findings challenge the assumption that LVR may influence VC. A longer period of LVR may be necessary to demonstrate an effect on slowing the decline in VC, if it exists.

Given the increase in LIC identified in this RCT, it is not surprising that the LVR group had an improvement in the LIC – VC difference over time. No change was found in the Control group, and there was a significant between-group difference. There was a strong relationship between change in LIC and LIC – VC in both treatment groups (LVR group r=0.83, Control r=0.86), suggesting that the change in LIC – VC difference is largely reflecting the change in LIC (Figure 8-22). Katz and colleagues also reported a 0.02 L/year improvement in the LIC – VC difference after initiating LVR which was sustained for up to ten years, and likewise attributed this to an increase in LIC over the first 4-5 years.[136] The authors further postulated that this increase in LIC – VC may indicate improvement in respiratory system compliance, as the LIC achieved reflects the volume delivered by applying positive pressure (e.g., via compression of a resuscitation bag). Therefore, greater LIC and hence LIC – VC difference for presumably the same driving pressure implies alteration in the pressure-volume characteristics (compliance) of the system.

Other authors have similarly postulated that MIC, LIC or the LIC – VC difference reflects "range of motion" or chest wall distensibility,[136,170,208,212,238] and that assisted inflation therapy may recruit areas of atelectasis, stretch contracted lung tissue, muscles and joints of the thoracic cage.[136,137,208,216,220] A number of landmark studies have measured static lung compliance,[66,143,147,149,159,160] dynamic lung compliance[145,146] or C_{rs}[78,152-155] in participants with NMD at a single point in time, but have not assessed LIC or LIC – VC. Furthermore, despite much of the clinical use of regular LVR being based on this theory, there has been no longitudinal research measuring compliance to investigate this assertion. This RCT does not convincingly support this hypothesis.

We did find that C_{rs} was related to VC in participants with more slowly-progressive disease, supporting the long-held view that lung and/or chest wall stiffness contributes to respiratory impairment. Moreover, the relationship between MIP and VC was weak in the Other NMD sub-group, supporting the seminal work that postulated that fixed restriction in the form of lung and chest wall stiffness may limit VC more than muscle strength in some people with NMD.[66,143,147,151,152] However, we found no relationship between the change in LIC and C_{rs} (Table 8-20, Appendix 11.5.9) or LIC – VC and C_{rs} at study start or end (data not shown), questioning the view that LIC is a surrogate marker of C_{rs}.

Despite having a stiff respiratory system, we found no conclusive evidence that this was affected by LVR. The observed improvement in C_{rs} over time, predominantly in people prescribed LVR, does raise the possibility of an effect on lung and chest wall distensibility. However, the linear mixed models for C_{rs} were not statistically significant overall and no between-treatment effects were noted. The lack of correlation between change in LIC and change in C_{rs} over the three-months (Figure 11-36) further supports this interpretation.

When specific C_{rs} was examined, to control for any concomitant change in lung volume, the model was statistically significant. Consistent with the C_{rs} findings, no treatment effect or between-group difference were present, however a main effect of time was apparent. Although the increase in specific C_{rs} was statistical significant in the LVR group, C_{rs} and specific C_{rs} improved in participants in both the intervention and active control groups (Appendix 11.5.4).

The increase in C_{rs} and specific C_{rs} over time could represent a beneficial effect of LVR and Breathing exercises in this study population but may also reflect a degree of measurement noise. We performed stringent analyses of the raw signals used to derive C_{rs} as detailed in Chapter 5, and obtained values similar to those published by Molgat-Seon and colleagues in a comparable NMD population suggesting validity of this method,[78] however we acknowledge this technique is not common. More conclusive results could be obtained with invasive compliance measurements using an oesophageal balloon catheter, which would have the advantage of differentiating

between intra- and extra-thoracic contributions. However, in people with substantial respiratory and physical disability such as in this cohort this assessment would be a technically difficult task and highly unlikely to be tolerated.

It is possible that the degree of respiratory system impairment of this cohort was too severe and/or long-standing to demonstrate an effect on C_{rs} or VC in the time frame studied. Median time since NMD symptom onset was 14.4 years, with group mean VC 1.58 ± 0.85 L (41 ± 19% predicted), MIP of 44 ± 26% and MEP of 42 ± 22%. Although previous studies have suggested an effect on VC in comparable or more-impaired participants, for example the DMD cohort of McKim and Katz had a median age of 19 years and mean FVC at LVR initiation of 14% predicted,[136,137] they were conducted over much longer periods.

It may be that a greater dose is required to influence underlying physiological change, especially in participants with slowly-progressive NMD spanning decades-long duration. The daily dose herein was selected with principles of exercise prescription in mind; the smallest dose found in existing literature of three maximal inflations twice a day did not intuitively address the proposed mechanism of "stretching" the respiratory system. The target prescription of 25 maximal inflations twice a day was greater than that previously reported (six to 45 inflations a day),[105,136,137,208,209,213,216,217,220,238,241] without seeming unrealistic for participants to incorporate into their daily routines. Dose also refers to duration of therapy however, and it may be this element which is required to effect physiological change, particularly in long-standing impairment of the respiratory system.

Whilst our data indicates that LVR does increase LIC and LIC – VC, the absence of effect on compartmental lung volumes and C_{rs} suggests that this improvement may not reflect benefit in respiratory system mechanics. Functional residual capacity did not change in either randomised group. Whilst differences were observed between the MND and Other NMD participants in keeping with the findings of Chapter 6, within these disease sub-groups, there was no effect of LVR or the active control. Similar results were observed for TLC, RV and ERV, with these volumes also remaining stable. Inspiratory capacity was the exception, with a significant fall over the three-months in

participants with MND in both randomised groups. This last finding is consistent with the progressive nature of the disease and the associated, observed decline in MIP and SNIP in this disease sub-group.

Had LVR recruited collapsed areas of lung, an increase in FRC may have been observed; in the presence of alveoli collapse, the measured static lung volume will under-estimate actual lung volume,[254] hence having more alveoli open at end-expiration will increase this. Re-expansion of lung tissue would therefore elevate *true* FRC, as well as the *measured* FRC. Increases in FRC would also be observed if the chest wall became more "flexible"; stretching of intercostal muscles, ligaments, tendons, costosternal and costovertebral joints would reduce elastic recoil, thereby elevating the resting position of the thorax.

This RCT identified statistically significant main effects of disease on MIP, MEP and SNIP. All inspiratory and expiratory respiratory muscle strength models demonstrated a decrease over time in participants with MND, whereas the Other NMD disease sub-group remained stable. The decrease reached statistical significance on exploratory analyses in the active control group of participants with MND; the non-significance in the MND, LVR sub-group likely represents a Type 2 error due to small numbers given both declined in absolute terms. Whilst there was a statistical between-group difference in participants with MND, only eight people in each arm limits the strength of any conclusions.

Given the decline in muscle strength and IC in participants with MND, it is not surprising that we also observed a reduction in PCF over time. These variables have been previously linked to PCF[100,168,171] and this relationship was confirmed in our sample (Chapter 6). Although the PCF models were not statistically significant overall, post-hoc analyses identified a main effect of time, with the largest decline in the MND, LVR group (-28 L/min, or 9.3 L/min/mth). This was more than the 5.8 L/min/mth decline observed by Rafiq and colleagues in their LVR group but could be due to our more severely affected cohort whose disease trajectory may have been faster. Median baseline PCF was 162 L/min in our MND participants, compared to 215 L/min, and other indices of disease severity were also reduced (mean VC %pn: 53% herein *vs.* 58%

Rafiq *et al*, ALSFRS-R = 24 *vs.* 29 points).[105] The PCF of participants with Other NMD did not change over the three-months regardless of randomisation group (Other NMD disease type = -7 (-19 to 5) L/min).

Whilst we found no change in PCF, there was an effect on $PCF_{LIC.}$ Model effects and a main effect of time were observed, with the increase largely attributable to the LVR group, and in particular the Other NMD, LVR sub-group. Although PCF_{LIC} was associated with LIC at a given timepoint (e.g., Figure 11-31 depicts baseline, final assessment illustrated in Figure 11-32), there was no relationship between the change in PCF_{LIC} and LIC. In this cohort, a smaller LIC was associated with a smaller PCF_{LIC} and larger LIC with a larger PCF_{LIC}, however *increasing* LIC did not translate into a higher PCF_{LIC}. This finding contrasts with current clinical belief; in one cohort study, the group that improved LIC over time also demonstrated an increase in assisted PCF despite falling VC and PCF, prompting the authors to conclude that a higher LIC is advantageous for obtaining a larger $PCF_{LIC.}$[208] Our results would suggest that whilst LIC and PCF_{LIC} are related, increasing LIC does not result in a linear improvement in PCF_{LIC}. A study by Mellies and Goebel corroborates this view. They incrementally increased assisted inflation volume in 40 participants with slowly-progressive NMD and found that the highest assisted PCF was obtained at a sub-maximal LIC, with the optimal insufflation capacity being 89-91% of maximal LIC.[99]

In the current study, the increase over time in PCF_{LIC} was strongly correlated with the improvement in PCF_{LIC} – PCF in the LVR group ($r=0.80$, $p<0.0001$), yet there was only a moderate relationship in the Control arm ($r=0.48$, $p=0.002$). Participants in the LVR group had a larger improvement in the PCF_{LIC} – PCF difference for a given increase in PCF_{LIC}. This implies that the LVR group is achieving a greater assisted PCF in the context of a declining unassisted PCF. Given there was no relationship between the improvement in PCF_{LIC} – PCF and the LIC – VC difference, this augmentation of expiratory flow during cough following a maximal inflation manoeuvre may not be attributable solely to greater inflation volume as commonly thought,[208] but to more practice and better coordination with the technique. A better understanding of how to perform LVR and 'hold' the insufflated volume prior to coughing may generate greater

intrathoracic pressure, recoil and thus expiratory flow, although this hypothesis remains to be tested.

Consistent with the finding that three-months of regular LVR did not change respiratory function such as lung volumes or C_{rs}, we found no effect on participants' generic overall HRQoL. Although we found a statistically significant drop in the psychometric score for the "Independent Living" domain over time, predominantly in the Control arm, this is likely to represent chance. When expressed as a health utility score, this was not statistically significant and confidence intervals were less than the 0.06-point minimal important difference (MID).[295] Comparable with the MID, a mean drop in Happiness health utility of 4% or -0.04 (-0.07, -0.01) units was observed in the LVR arm, with significant decline also in the MND disease sub-group (Figure 11-16). This may represent disease progression and deteriorating function in the latter, as evidenced by the decline in VC and ALSFRS-R scores. In order to understand whether routinely performing LVR does indeed impact on Happiness, further qualitative research is needed.

Similarly, we found no change in disease-specific HRQoL or respiratory symptoms over the three-month study duration. The baseline SRI summary score of this cohort (mean = 44 ± 9 points) was slightly lower than that of NMD populations represented in previous literature, whereby mean scores have ranged from 49 points to 59 points,[276,282] and may reflect the severity of respiratory impairment.

Sub-group analysis of 22 participants with MND and pre-post SRI data did however suggest improvement, with a mean increase of 5 (1, 9) points observed. Although no MID has been established for the NMD patient population to date, this improvement lies within the MID range of 5 to 7 points reported for severe stable COPD.[296] Furthermore, it is of similar magnitude relative to that described in a NMD population one-year post NIV.[276] This increase in participants with MND, regardless of treatment group, may reflect improvement in the Social Functioning (e.g., ability to take part in social activities) and Respiratory Complaints (e.g., shortness of breath) domains, perhaps related to more frequent contact with clinicians and assessment of respiratory

function as part of the study period. However, given the exploratory nature of the analyses in this smaller sub-group this supposition is purely speculative.

The stability of QoL over the study period is promising; therapies may add stress and complexity to an already elaborate or time-consuming health care routine, hence interventions need to be "worthwhile" for the individual. The longer-term cohort studies did not include QoL or patient-reported outcome measures,[136,137,208,209,216,242] nor did the trial by Marques and colleagues.[213] This RCT is one of the few trials that has evaluated QoL; a year-long study involving participants with MND[105] and a three-month feasibility study[220] both found no change in HRQoL. Whilst the trial by Rafiq and colleagues also reported no change in carer strain,[105] interestingly 10 of 24 participants involved in the shorter study were not willing to continue daily LVR at study completion. Reasons included no perceived benefit, too uncomfortable, too difficult and performing routine treatment emphasized illness.[220] A follow-up qualitative study of current trial participants has been conducted and will inform the discussion regarding perceived benefit and burden of undertaking regular respiratory therapy, but more work is needed in this area

9.2 CLINICAL SIGNIFICANCE

Although this RCT found an increase in LIC with regular LVR, the clinical significance of this finding is not clear. There were no beneficial effects of improving LIC or performing LVR on VC or compartmental lung volumes over the three-month study duration. Similarly, there was no clear benefit in C_{rs}; C_{rs} did improve over time, however this was not irrefutably attributable to LVR. Furthermore, whilst LIC increased by more than 10% in the LVR group and was associated with an increase in the LIC – VC difference, implying that participants could recruit more volume, this was not correlated with improvement in C_{rs}. We found no conclusive evidence that LIC or the LIC – VC difference are surrogate measures of respiratory system distensibility, nor that increases in these outcomes signify improved compliance.

An increase in LIC could potentially signify improvement in respiratory muscle strength or recoil of the respiratory system as the manoeuvre requires participants to actively exhale fully to RV. However our data does not support this mechanism either; MEP remained stable or declined over the study period.

Over the study duration the cohort increased PCF_{LIC}; there was no treatment effect but this finding was predominantly due to participants in the LVR group. As with the improvement in LIC, the clinical significance of this result is not known. The primary aim of this RCT was not to assess the effect of LVR on sputum or airway secretion expectoration, hence we did not measure sputum yield or radio-labelled aerosol clearance of secretions. Furthermore, we did not ask participants to rate the strength or ability of their cough to clear mucus, so can not assess participant-perceived cough effectiveness. However, we found no significant change in HRQoL measures, including the SRI Respiratory complaints domain which focuses on the impact of breathlessness and sputum on daily living, to indicate that performing LVR, increasing LIC or PCF_{LIC} translates to improved clearance of secretions.

Consensus opinion asserts that PCF is a marker of "cough effectiveness",[13,53,134] yet there are no data linking PCF to airway clearance. Peak cough flow measures the flow of air as it is expelled from the mouth, not gas linear velocity, and there is no data that correlates these two units during a cough. Rather, a mechanical model has demonstrated that it is the velocity of the initial accelerative spike that is primarily responsible for particle displacement rather than the sustained flow phase.[89] Work in participants with chronic lung disease further challenges the view that PCF is a marker of "cough effectiveness". Both a volitional cough and a huff increased clearance of inhaled radio-labelled aerosol particles and sputum yield compared to control, however a huff achieved airway clearance at lower (203 ± 25 L/min *vs.* 288 ± 29 L/min)[92,93] or comparable (174 ± 30 *vs.* 192 ± 30 L/min)[95] PCF values. Doubling supramaximal flow rates *beyond* the supramaximal rate usually witnessed with a volitional cough (564 ± 120 *vs.* 246 ± 114 L/min) similarly did not enhance radio-labelled aerosol clearance,[95] suggesting that it is the presence of a spike rather than the absolute value that may be important.

Furthermore, there is data to suggest that changes in PCF do not reflect changes in cough mechanics. The PCF values produced during different cough types (volitional, spontaneous and laryngeal coughs) differ significantly,[84,130] yet oesophageal (P_{oes}) and gastric pressures (P_{ga}) are comparable.[88,124,130] Another group has used incremental paralysis of expiratory muscles via curarisation to mimic declining expiratory muscle strength; whilst P_{pl} decreased in proportion to maximal expiratory pressure (MEP) with concomitant loss of cough spikes, no change in the maximal flow (i.e., PCF) was observed until the final dose of *d*-tubocurarine.[87] Conversely, it has been shown that PCF increases incrementally with increasing operating volume, with no concomitant change in P_{oes}, P_{ga} or transdiaphragmatic (P_{di}) pressure.[88] These findings collectively support the assertion that PCF does not adequately assess the physiological elements of cough that are likely important for airway clearance, namely intrathoracic pressure, gas linear velocity and the presence of supramaximal flow.

Notwithstanding these limitations, PCF has considerable currency. Guidelines recommend it be routinely assessed along with other respiratory function tests and in some jurisdictions, low PCF values guide treatment prescription.[10-13,15,187,195,297] Whilst P_{pl} (i.e., P_{oes}) P_{ga}, P_{di} or cough gastric pressure[181,255] may better assess cough mechanics, these techniques are invasive thereby limiting clinical feasibility. Interest in other non-invasive measures is growing, including cough sound power[298] and metrics derived from cough flow waveforms; inspiratory phase duration, peak inspiratory flow rate, compression phase duration, peak expiratory flow rise time (analogous with expiratory rise time or peak velocity time), cough expired volume and cough volume acceleration.[128,131,290,299] It has been suggested that peak velocity time and cough volume acceleration assess laryngeal function, can detect glottic dysfunction and risk of aspiration,[290,300] but whether these outcomes better quantify airway clearance has yet to be investigated.

The absence of physiological improvement suggests that the outcome measures employed in this trial were not sensitive enough to detect change, or that the mechanism of effect over this time period is not via improved respiratory physiology. The LVR counter data and dose-response elements of this RCT would support this

interpretation; not all those participants in the intervention arm performed LVR as prescribed, yet we still found a group mean increase. Moreover, no relationship was present between use (either self-reported or recorded) and change in respiratory function, implying that the magnitude of effect was not dependent on therapy dose.

It is possible, given the findings of Chapter 7, that an increase in LIC could be found if participants in the LVR arm performed a therapy session immediately prior to their final assessment. The mean improvement in LIC following a single-session of LVR in naïve participants was 130 mL (50, 210 mL); approximating the increase of 130 (10, 240) mL observed in the LVR group over three-months. As such, all of the difference we attributed to the RCT intervention could have been an artefact. However, only three of the 33 people in the intervention arm who attended this last visit performed a LVR session prior to testing on that last morning. These three sessions were 58 seconds, 3 minutes 25 seconds, and 7 minutes 56 seconds respectively in duration and were all completed at least two hours before data collection. Previous work has demonstrated that immediate LVR effects are not present 60 minutes later,[78] therefore it is highly unlikely that these therapy sessions had a carry-over effect on the outcome measures and the 130mL mean improvement observed over three months likely represents a real change.

The participants in this study were naïve to LVR and measuring LIC, thus improvement over time could reflect a test-retest practice effect. The LVR group were not more practised at the LIC test *per se* because all participants regardless of treatment group underwent the same standardised testing procedure. However, by virtue of performing their randomised therapy, the LVR group had greater exposure to the technique and attaining LIC. The linear mixed model demonstrated that the largest increase in LIC occurred by the first follow-up assessment, one-month after randomisation (Figure 8-6). This finding alone does not exclude a change in pulmonary mechanics, however the time course is consistent with the hypothesis that participants performing regular LVR may be acclimatising to the sensation of being inflated. We found no difference in the peak inspiratory pressure at LIC at Timepoint 3a compared to Timepoint 0a between the LVR or Control groups (Table 8-21), however there was a

stronger relationship between improvement in LIC and pressure reached in the intervention arm. Tolerating higher pressures may therefore be one factor contributing to the observed increase in LIC over time.

The contradiction between the immediate response observed in the cohort at study commencement compared to the final assessment (Section 8.13) substantiates the thesis that initial improvements may be attributable to a skill acquisition effect. Whereas a single-session of LVR improved LIC, PCF_{LIC}, LIC – VC and PCF_{LIC} – PCF in naïve participants (Chapter 7), this effect was absent after three-months in both treatment groups (Section 8.12). This strongly suggests that the improvement in LIC observed after the initial single-session was attributable to learning the technique, including how to coordinate bag compressions with the individual's intrinsic pattern of respiration, familiarisation with the sensation of being insufflated and/or confidence to achieve the maximal, tolerable insufflation capacity.

Exploratory post-hoc analyses strengthen the argument for a learning effect influencing the study's main finding of an improvement in LIC. Prior to randomisation, this naïve group as a whole demonstrated a statistically significant increase in LIC following a short standardised LVR session at the initial assessment (mean increase 0.13 (0.05, 0.21) L, p=0.002). Pairwise comparisons suggest that LIC improved from Timepoint 0a to 0b primarily in participants who, by chance, were subsequently randomised to the LVR group (Table 8-22). Lung insufflation capacity was maintained for the three-month RCT duration but did not improve further from Timepoint 0b. In contrast, participants who were randomly allocated to the control arm showed no immediate change in LIC, nor change over three months using either Timepoint 0a or 0b as "baseline". These data imply that *pre-randomisation* and therefore purely by chance, the intervention group had an improvement in the primary outcome consistent with a measurement learning effect, that was not evident in participants assigned to the active control group.

We found no evidence of an immediate physiological effect of LVR on LIC, VC, LIC – VC, C_{rs}, specific C_{rs}, PCF_{LIC} or PCF_{LIC} – PCF, in participants at study conclusion. Statistically significant declines in FRC and TLC were observed following the single LVR session, predominantly attributable to participants with MND regardless of RCT group. A fall in PCF after the single-session was also found (Table 8-15, Table 8-16), with post-hoc analysis suggesting this may be more so in participants with Other NMDs or in the LVR intervention (Table 11-30). These decreases may represent fatigue in this moderately to severely impaired cohort, particularly in participants with MND and concomitant disease progression; at study commencement, 93% of participants with MND could perform the single LVR session and subsequent post-session testing, compared to 78% at the final assessment.

The conclusion that respiratory function does not improve immediately after LVR when performed in participants who are not acutely unwell complements existing data. A study in healthy participants found that whilst LVR can increase end-inspiratory chest wall volume during the manoeuvre, there appears to be no carry-over to IC, VC or PCF post therapy.[228] Similarly, Molgat-Seon and colleagues showed no change in VC or PCF in 12 participants with slowly-progressive NMD following a session of LVR at equivalent dosage to the current study (10 maximal inflation breaths).[78] They did however report a transient increase in C_{rs}; our larger sample (60 participants with paired C_{rs} measurements) and/or measurement variability may explain why we found no effect on C_{rs} when LVR was performed by participants no longer naïve to the therapy.

Other studies using alternative methods to deliver comparable hyperinflation therapy, such as IPPB, a MI-E device or NIV corroborate that a single-session of hyperinflation therapy does not change VC, FRC, compliance or PCF.[154,156,159,230,231,235]. One study did report an immediate increase in VC, however the magnitude of effect was small (108 + 7% of baseline) and reverted within an hour,[234] hence the clinical significance of this finding is questionable. Another demonstrated improved lung ventilation on electrical impedence tomography following IPPB; whether this translates to improved lung volumes and/or compliance is unknown.[233] Previous research comprised small

participant numbers (ranging from 9 to 20), but collectively they support the findings of the current larger study, that a single-session of assisted inflation therapy does not improve respiratory function in medically stable participants.

Whether LVR has an immediate physiological effect during an acute RTI remains to be seen and should be the focus of future studies concentrating on short-term use. There is no prospective controlled research evaluating volume recruitment during an acute episode in participants with NMD, however case reports or cohort studies indicate that cough augmentation and treatment with assisted inflation is safe and effective during such times.[172,301-304] Three of these studies included LVR treatments, although MI-E was predominantly employed. Comparison between MI-E and LVR in 9 patients with PPS suggested that the mechanical device increased inflation capacity and assisted PCF more than LVR.[303] Two prospective cohort studies of people with MND or other NMDs admitted with an acute RTI have reported high rates of treatment success (79%) using non-invasive aids.[172,304] In one centre, inpatient therapy consisted of NIV plus MI-E for mucus expectoration, switching to LVR as clinical status improved.[304] Mechanical insufflation-exsufflation was also preferred in the acute stage in people with MND; 92% of the cohort were managed with MI-E compared to LVR (4%). In addition, the authors also found that a PCF greater than 166 L/min during an acute RTI was the best predictor of whether a person's unassisted cough could effectively clear secretions, one of the few studies to demonstrate a relationship between PCF and clinical outcomes.[172] Based on these limited data and consensus opinion,[10,13,187] MI-E is the treatment of choice during periods of acute illness, however prospective studies comparing the effectiveness of LVR with MI-E are required to provide evidence for this practice.

Our RCT findings imply that underlying change in respiratory mechanics may not occur within a three-month timeframe. Nonetheless participants did obtain a higher LIC, even if the mechanism was via a learning effect or tolerating higher pressures as speculated, and there may be other clinical benefits associated with this such as reducing the risk of RTIs.

Lung volume recruitment and/or assisted inflation therapies feature in many NMD clinical care recommendations. The British Thoracic Society guidelines for the respiratory management of children with a neuromuscular weakness note that breath-stacking methods should be used when appropriate to improve cough efficiency;[13] the latest guidelines for patients with SMA recommend that airway clearance techniques (primarily MI-E) be introduced proactively and "made available to all non-sitters"; [14] whilst it is recommended people living with DMD do LVR once or twice daily to preserve lung compliance, once FVC <60% predicted.[15] Regarding management for adults with a NMD, the British Thoracic Society advocates that lung inflation exercises be considered three times per day once VC <2 litres or less than 50% predicted when patients are well with PCF >270 L/min, plus ACTs should be employed once PCF <270 L/min, patients have difficulty clearing secretions, or they are unwell with a cold.[12] Similar recommendations are made by the Canadian Thoracic Society[16] and the Spanish Society of Pulmonology and Thoracic Surgery,[17] with both referring specifically to LVR. Meanwhile, the American Academy of Neurology practice parameter update for the care of the patient with ALS recommends cough augmentation assistance when PCF <270 L/min.[187] These statements reflect the prevailing clinical opinion that regular assisted inflation therapy enhances cough effectiveness, maintains or slows respiratory function decline and prevents RTIs.

This RCT has generated preliminary data that suggests three-months of regular LVR does not modify respiratory function in a severely restricted cohort, however forming conclusions regarding the use of regular LVR to prevent RTIs from this study is not wise as this was not our primary hypothesis. As evidenced by the prevalence of RTI in our baseline data and a year-long RCT, the event rate of acute respiratory complication is low in this population,[105] despite respiratory morbidity being of grave concern.[305] The RTI event rate in the study conducted by Rafiq and colleagues was lower than anticipated, hence no conclusions as to whether respiratory therapies reduce RTI could be made; based on their findings a sample size exceeding 200 participants would be required to detect a difference in RTIs (risk reduction of 0.5).[105]

In the current, relatively short-duration RCT, we found no difference in the number of primary care or hospital admissions between the LVR and active control groups. Overall the prospective incidence of RTI-related episodes was 0.12 episodes/participant/3-months, similar to the 0.60 episodes/participant/year reported retrospectively in the year prior to study enrolment. Clearly longer and much larger prospective cohort studies are required.

Regular practice of LVR may familiarise the person with the technique, so that they are more skilled to employ it when needed, such as for cough augmentation or during a RTI. Although we found no carry-over of regular LVR to the immediate response in participants who are well, we did see a larger "cough augmentation" effect (PCF_{LIC} – PCF difference). Whether this translates to improved airway clearance or lung volume recruitment during acute illness is an area requiring reseach. Clinical rationale exists for using volume recruitment techniques during acute respiratory compromise; extrapolating from intubated and ventilated patients, hyperinflation therapies can increase lung volume, sputum clearance and C_{rs}.[19-21] Whilst there are no prospective controlled or comparative studies, case reports have described successful management of patients with NMD using NIV, MI-E and LVR during acute RTI,[172,301-304] and based on clinical opinion this practice is recommended during acute periods.[14,15]

Nonetheless, this research project does question whether regular LVR is necessary to be familiar with therapy. Although we found some evidence of a 'learning curve', this appears to be short; LVR is an easy technique that does not require substantial skill acquisition when initiated by an experienced clinician and participants are well. Furthermore, domiciliary NIV use, disease type and/or bulbar dysfunction did not appear to limit the success of this technique.

This study did not investigate the optimal learning period, but we postulate that it is short. The LIC – VC difference expressed as a percentage of VC increased from 37±46% to 46±44% for the cohort as a whole after the training session, with mean values of 49±42% and 49±56% observed in the LVR and Control groups after three-months (data in Appendix 11.5.3). This measurement is an indication of how much additional volume can be insufflated; a larger value could reflect short-term learning, becoming more

proficient with repeated practice, or physiological change. Based on these and the time course of change in LIC (explored in Section 8.14), we postulate that participants gain basic competency within one study visit.

In addition to the clinical significance of an increase in LIC, this study also provides valuable information on the clinical feasibility of performing regular therapies. Lung volume recruitment was well tolerated, with no adverse events occurring during this RCT. Participants in both treatment arms did report side effects, categorised into three main themes: shortness of breath, dizziness, or musculoskeletal discomfort. Side effects were experienced by 29% of the cohort and in all but one case were mild, intermittent and/or resolved with additional clinical review to titrate exercises.

These findings are consistent with previous literature that suggests complications associated with LVR and/or other assisted inflation therapies are few. Abdominal bloating, nausea and abdominal distention have been documented with MI-E,[10] and haemodynamic responses have also be observed. In one study investigating the immediate effect of LVR, therapy elicited a transient reduction in mean arterial blood pressure (MAP) that was associated with symptoms such as light-headedness in a quarter of individuals.[78] This is likely due to the increase in intrathoracic pressure, as blood pressure returned to normal values within seconds of exhaling from MIC. Similar findings have been reported with glossopharyngeal breathing; a transient increase in heart rate and fall in MAP was seen in participants with SCI and healthy controls.[226]

Although rare, the most serious complication is undoubtedly a pneumothorax. A number of case reports now exist of this occurring in people with NMD using positive pressure, whether that be in the form of LVR, MI-E, NIV or combinations of these.[306-310] However, the precise rate of pneumothorax is unknown as longitudinal data is lacking. Reports examining the long-term effects of LVR have not reported any serious adverse events, suggesting a low event rate.[105,136,137,208,209,213,217,220]

Concordance with the prescribed routine of twice-daily therapy was reported to have occurred 45% of the time if randomised to LVR, compared to 75% in the Control arm (p=0.060). On average, participants reported performing 1.2 sessions / day of LVR

versus 1.5 sessions / day of the active control breathing exercises (p=0.015). There was strong agreement between the number of sessions reported by the LVR participants and the data downloaded from their LVR counters (Rho_{CCC} = 0.88 (0.80, 0.95), Pearson's r = 0.91, p<0.0001). This implies that self-report by diary was representative in this study, with the caveat that participants knew they were also being monitored. Measurement bias favoured self-report, suggesting that at times, participants either reported more sessions than they performed, or the LVR counter was not turned on prior to exercising. Based on the LVR counter data, participants performed an average 1.0 session / day.

This study is the first to use an objective measurement of therapy use, and suggests that there are barriers to regular LVR requiring further investigation. Whilst over a third of participants performed at least one LVR session a day on more than 85% of days, a third of participants did not perform LVR at all, for at least half of the study days (Section 8.4.2). This disparity, in a research trial environment where participants were aware that use was being monitored, provides valuable insight into the uptake of therapy prescribed by clinicians. It informs discussion about the feasibility of regular therapy in this patient population and confirms that measures of use and participant experience are necessary in future studies.

9.3 STRENGTHS AND LIMITATIONS

The current research is the first study of regular LVR to include a control arm for comparison, which given the natural course of these progressive diseases, is crucial for interpretation of the findings. The LVR and active control arms were well matched for baseline characteristics and stratifying by disease-type resulted in an equal representation of conditions in the treatment groups, which we *a priori* hypothesised may respond differently. Justifying this design decision, we observed relentless disease progression in the MND sub-group, as evidenced by significant decline in the ALSFRS-R in both treatment groups. Rate of decline over the three-month study period was -5.5 (-7.6, -3.5) units, or -1.8 (-2.5, -1.2) units per month; greater than the -0.92 (standard

error = 0.08) per month observed in the NEALS (Northeast ALS Consortium) clinical trials database,[311] with no treatment effect or treatment by time interaction evident.

The only other RCTs published to date have not comprised a control arm or been in a considerably different patient group. The first investigated the effect of twice-daily LVR compared to MI-E over a 12-month period in participants with MND. This commenced at the time of NIV initiation, potentially confounding findings.[105] In the current study, participants were established on NIV for at least three months prior to randomisation thereby minimising the influence of NIV on study outcomes. The RCT by Jeong and colleagues compared six weeks of LVR to incentive spirometry in participants with recent SCI, a population different to medically-stable progressive NMD.[241] In both trials, physiological measures of respiratory function were limited to VC and PCF.

For this RCT, a routine of breathing exercises was selected as the active control arm. It could be argued that this treatment conferred some benefit, thereby minimising between-group differences and masking a LVR intervention effect. However, research examining breathing exercises similar to the active control treatment would refute this assertion. Whilst deep breaths can increase inspired volume compared to tidal breathing in participants with long-standing SCI and respiratory muscle weakness, maximal obtainable TLC is not reached by such exercises, and no change in FRC is apparent.[312] Findings from a pilot study of eight people with MND who performed breathing exercises more frequently than prescribed herein similarly suggested no carry-over effect, with no change in FVC or the FVC Slope observed after three-months.[313] A cross-over trial of inspiratory muscle training versus deep breathing in 21 participants with muscular dystrophy also found no difference in VC over a three-month training period, although MIP and MEP increased after the muscle training intervention.[200] In healthy subjects, diaphragmatic breathing of the type used here was associated with thoraco-abdominal asynchrony and did not approach the chest wall volume achieved by “inspiratory sighs” (stacking via nasal sniffs).[314] It is improbable that exercises that produce sub-maximal inspired volumes in people with unaffected respiratory muscles would generate an inspired volume approximating IC when performed by people with respiratory muscle weakness. As such, the active control

treatment is highly unlikely to influence the primary or secondary physiological outcome measures examined in this research project.

The current study obtained data for the primary analysis in 72 participants, commensurate with the sample size required to detect a between-group difference. The 76 randomised participants prospectively followed represents the largest clinical trial to date, doubling to quadrupling prior efforts.[105,213,220,241] Despite involvement of the state's paediatric neuromuscular centre, this study did not enrol any participants under the age of 18 years, and therefore reflects an adult NMD population. Whether similar effects of regular LVR occur in children with congenital NMDs remains to be shown, however a retrospective cohort study of 21 paediatric participants (mean age of 16 years) who performed assisted inflations via MI-E did demonstrate improvements in VC within the first year post-initiation.[242] A RCT of LVR compared to conventional treatment in children with DMD aged 6 to 16 years, has been completed with results pending, and will inform this question (www.clinicaltrials.gov/ct2/show/record/NCT01999075).

This work focussed on respiratory physiology as the first, necessary step to understand the fundamental efficacy of therapies such as LVR. The selected respiratory function tests represented a balance between clinical practice, feasibility and physiology. A fitting example is the use of MIP, MEP and SNIP to infer respiratory muscle strength; these tests are often measured in clinical practice and are clinically useful, however they approximate global respiratory muscle strength and are not direct measures of diaphragm strength. Other invasive methods such are measuring P_{oes} and P_{ga} to arithmetically derive P_{di} during static and sniff manoeuvres, diaphragm electromyography or magnetic phrenic nerve stimulation and twitch diaphragm pressure are more sensitive measures,[134,315] however they are arguably less well-tolerated by participants and less well-known by clinicians, therefore potentially limiting study recruitment, retention, applicability and translation of this work to a clinical setting.

It is also acknowledged that many of the respiratory outcomes conducted are subject to participant effort, fatigue, technique and practice. In order to control these factors

as much as possible, standardised testing procedures and assessment of test acceptability were undertaken, a set of scoring rules were developed for C_{rs}, and a single assessor performed all baseline and final assessments to preclude inter-assessor variance.

The limitations of PCF as a measure of cough "effectiveness" were explored in Section 2.3.4.1; notwithstanding these issues PCF was selected for this research project to enable comparison with prior research. Participants were instructed to "produce their biggest, strongest cough", with no reference to the pre-cough inspired volume. Hence each individual determined whether they inspired fully to TLC or took a sub-maximal inspiration to achieve their strongest cough. We decided not to standardise pre-cough inspired volume and instead focussed on maximal effort, as a review of literature identified disparity in the operating volume from which a cough occurs (50% of V_T to 90% of TLC).[85-87] Subsequent to the study protocol and commencement date, an expert group defined an unassisted PCF as a cough from the "maximum, unassisted inspiratory lung volume (i.e., to take a deep breath in prior to coughing)".[10] Although the PCF measured herein does not conform to this consensus definition, the procedure used was standardised, well-described and is repeatable by others. Clearly more research is required to identify and standardise measures that assess cough function, including whether markers accurately assess the ability to clear sputum and protect the airway.

Our definition of an assisted PCF does match that of the consensus group, being a "cough from their maximum, assisted inspiratory volume".[10] This study initially intended to measure "assisted PCF" as the peak expiratory flow rate of a cough following "breath-stacking plus manually assisted cough". However, the first five study participants all had a gastrostomy feeding tube in situ and declined a MAC, hence assisted PCF was performed from LIC only. Although this deviated from the original study protocol / ANZCTR-listed definition, this method is arguably more robust as it standardised the amount of assistance provided; a MAC provides variable assistance depending on care-giver technique and is not reproducible. The terminology "peak

cough flow from LIC (PCF_{LIC})" was thus adopted for the entire study to more accurately describe the assisted PCF manoeuvre conducted.

Attesting to the preciseness of this research project, two other outcomes were also re-labelled to better match the actual test procedures; this study was prospectively registered with the ANZCTR on 1/6/2015, and listed "maximal insufflation capacity (MIC)" and "forced vital capacity (FVC)" as outcome measures. However, correct terminology has been applied throughout this thesis, namely "lung insufflation capacity (LIC)" and "vital capacity (VC)".

Three-months of LVR is arguably not long enough to produce detectable change, especially in long-standing and/or slowly-progressive NMDs such as DMD or SMA. Duration is only one factor influencing treatment response however; the combination of severity and chronicity of restriction at LVR initiation, developmental growth stage, underlying disease trajectory, daily dose *and* duration are likely to be intricately linked. Whilst LVR was performed for a median of 3.75 years in the initial cohort study that suggested slower rate of FVC decline, the daily dose was much lower and participants more severely restricted when they commenced regular therapy than herein.[137] In this RCT, a shorter but more intensive dosage was adopted, with the hypothesis that some degree of physiological change may be demonstrable in this timeframe.

Given the improvement in LIC and LIC-FVC observed by Kaminska and colleagues,[220] the three-month study duration was deemed an acceptable therapeutic period over which change may be detectable whilst balancing concerns regarding clinical and ethical equipoise. Regular respiratory therapy was not standard clinical practice for adult patients with NMD managed by this specialist respiratory centre at the time the RCT began, hence there was clinical equipoise to conduct this study. The lack of controlled trials demonstrating benefit of treatment underpinned this local practice. Absence of evidence has also been identified as a factor limiting uptake in Canada, where regular LVR is offered by less than 20% of clinicians to approximately a third of patients with DMD despite national and disease-specific guidelines existing,[316-318] further highlighting the need for research in this area.

Nonetheless, the shift in consensus statements toward prophylactic measures that recommend people commence once to thrice daily LVR when FVC or PCF falls below defined thresholds when well[12,15,16] was identified as a potential barrier to recruitment, even if not based on robust science. We were cognisant that people living with NMD may not wish to participate in a longer study, whether that be due to a perceived risk of missing out on the intervention, or other barriers such as time commitment or care requirements limiting ease of participation. Furthermore, a three-month study duration was considered ethical in a rapidly-progressive disease such as MND; at the end of this time all participants were offered LVR, thus providing an opportunity to confer benefit if indeed it was found to be efficacious.

9.4 AREAS FOR FUTURE RESEARCH

The absence of an effect on VC, lung volumes or C_{rs} in this study does not exclude the possibility that regular LVR may maintain or slow the decline in respiratory function if performed for longer or perhaps earlier in the disease course. Rather, the study findings inform future research to be undertaken.

Respiratory system compliance was an integral component of this research project; C_{rs} analysis at baseline demonstrated lower compliance in participants with Other NMD than those with MND and was associated with VC. Being able to measure C_{rs} in a clinical environment is essential; much like using decline in FVC to guide therapies, knowing the course of C_{rs} and assessing response could have great clinical utility. The pulse method of measuring C_{rs} employed for this RCT was non-invasive and could be conducted in participants' homes, however it does require specialised equipment, limiting its clinical applicability. During the instrumentation and methods development phase of this research project, a novel technique for measuring C_{rs} was identified that requires less equipment and may better reflect static compliance. This technique uses the step-wise increments of volume and pressure, measured during periods of plateau flow achieved during LVR, to construct a pressure-volume curve, the slope of which reflects C_{rs}. Preliminary experiments and analysis have demonstrated feasibility, and

further work is planned to develop and validate this technique, potentially resulting in a non-invasive, ambulatory measure of C_{rs} that can be used in a clinical setting.

Further analysis exploring the relationship between LIC or the LIC – VC difference and C_{rs} is also planned. It has been proposed by Bach, Kang and others that LIC reflects "range of motion", and that assisting inflation to the participant's maximum, tolerable insufflation capacity is analogous to "passive range".[136,170,208,212,238] This thesis has presented some data that would refute this, however utilising the comprehensive dataset collected across all four timepoints would inform this discussion further. Furthermore, data from this trial could be used to evaluate how efficacious assisted inflation is at increasing volume to or beyond the theoretical "active range", by analysing the LIC obtained and expressing it as a percentage of each individual's predicted spontaneous TLC. Given multi-breath nitrogen washout was collected at each timepoint, it is also possible to determine lung clearance index and normalised phase three slope analysis for this dataset. These ventilation distribution indices provide information on ventilation inhomogeneity, which may be more sensitive to change over time compared to lung volumes.[254]

The need for future research to be conducted in the field of "cough" has similarly been highlighted by this research project. As discussed throughout this thesis, the most common metric used to measure cough is currently PCF, however there are many unanswered questions; including the effect of operating volume, interface and device on PCF obtained. A standardised procedure, knowledge of intra-participant test-retest variability and normal healthy values are required, as exists for other respiratory function tests. Our existing data provides some preliminary information regarding measurement error and/or the inherent variability of PCF that could be used to inform future studies; PCF was unchanged across the pre-post intervention study at three-months in participants with Other NMD, with a mean difference of -7 (-19 to 5) L/min (Figure in Appendix 11.5.6). It would also be valuable to analyse the relationship between cough metrics including the pre-cough inspired and exhaled volume for each cough manoeuvre, to add to our understanding of cough mechanics.

Arguably however, the first and broader research question should be to determine appropriate marker/s of "cough effectiveness"; although there is physiological justification for cough to be affected in people with NMD, data quantifying and exploring these mechanisms is lacking. Evident from Sections 2.3.4 and 2.4.1, a cough is a complex manoeuvre with important roles in airway clearance and airway protection. Peak expiratory flow measured at the mouth is unlikely to adequately reflect these functions.[92-95] We propose an experiment that assesses cough spirometric measurements, during reflex, spontaneous and volitional cough manoeuvres in healthy and NMD-affected participants. Relating these to participant-perceived cough effectiveness would provide information regarding possible metrics and subjective ability to clear secretions. Promising outcome measures should then be validated against physiological markers such as intrathoracic pressure generated during cough and radio-labelled aerosol particle clearance. To evaluate airway protection and cough effectiveness in participants with evidence of aspiration, applying the Penetration-Aspiration Scale to videofluoroscopic swallowing studies may be useful.[319] Ultimately, a prospective, longitudinal study comprising serial cough measures, respiratory function tests and clinical outcomes such as need for and timing of NIV, ACT and incidence of RTI is required to determine the clinical significance of these.

Moreover, a longitudinal study assessing C_{rs}, lung volumes and respiratory muscle strength is also necessary to better understand the time-course and mechanism of change in respiratory function in people with NMD. We speculate based on the baseline data from this research project, that muscle weakness may be an important determinant of lung capacity initially, with stiffness contributing more to the restriction seen as NMDs progress over time. Longitudinal data would investigate this hypothesis, as well as whether respiratory function measures are able to predict people with NMD at risk of developing a RTI.

This RCT found no suggestion of a dose-response, however exploratory analyses of baseline characteristics of "responders", that is those participants in the LVR arm who demonstrated a significant response, has not yet been undertaken. It has been postulated that individuals with higher baseline lung function may not respond to

regular LVR, whereas greater "recruitability" (i.e., LIC – VC difference) may be related to longer-term effect.[217] However the discriminatory ability of baseline measures to predict longer-term benefit has not been assessed. It is plausible that there are characteristics observable at LVR initiation that may be associated with responders, enabling more targeted prescription to patients in clinical practice and informing future trial design.

Valuable lessons have been learnt from this RCT which should inform replica and/or follow-on studies. Exploratory analyses suggested that disease-type likely influences the effects observed; we stratified randomisation in the current study to account for this, however future trials may wish to consider other approaches. Future studies may not require the full protocol of comprehensive respiratory function assessments in every participant; static lung volumes in particular required additional specialised equipment, were time-consuming and arduous for some participants to perform, resulting in incomplete data. However, there is a pressing need for studies to identify and evaluate the outcomes that are of greatest importance to people living with NMD, including but not limited to more in-depth qualitative data, patient-reported outcome and experience measures. Anecdotally, some patients report that regular therapy reduces dyspnoea, improves voice, the ability to cough and clear secretions; these and/or other clinical outcomes such as reducing RTIs or delaying the need for ventilatory support need to be addressed in future studies.

This RCT has provided proof-of-concept for LVR, a technique that is feasible in many jurisdictions. However, other assisted inflation therapies are in clinical circulation and require evaluation, the most obvious being MI-E. This study selected LVR over the MI component of a MI-E device, as it is widely accessible, inexpensive and available in a wide range of health care environments. Furthermore, we wished to assess assisted inflation alone compared to a control arm before evaluating a "combination" therapy. Follow-up studies should investigate whether the advantages of MI-E (e.g., less manual operation required, can deliver exsufflation component, may be more effective during acute RTI) outweigh access and cost issues, and/or matter on important patient-reported outcome measures.

Given current advances in the pharmacological management of conditions such as SMA (and potentially MND in the years to come), the concomitant change in clinical presentation, shift in care objectives and growth in international recommendations, it is doubtful that a RCT design of adequate duration can be conducted to answer the questions raised above. Prospective longitudinal studies with *a priori* hypotheses, in larger numbers of people living with NMD are likely to be required. Models for this approach already exist, for example the 20-year cohort study by Berlowitz and colleagues examining the effect of NIV on survival in MND,[4] and the work by Rose *et al* quantifying healthcare utilisation in a Canadian adult NMD cohort.[28] Reaching consensus on respiratory outcomes, collecting respiratory function regularly as part of standardised clinical care, recording this in a national NMD registry, utilising hospital presentation and other "big data" and collaborating widely is imperative, with smaller quantitative and qualitative comparative clinical trials complementing this program of research.

Finally, this RCT has highlighted what we believe to be two fundamental research concepts; the need for an objective measure of therapy use, and the value of in-home assessments. The former provided valuable data to evaluate concordance with prescription and aid interpretation of possible mechanisms of effect. Furthermore, objective use of LVR has generated some preliminary information, which will be used alongside the pending qualitative data to speculate and generate hypotheses regarding participant acceptability. The benefit of conducting in-home data collection for half of the study visits is less tangible, however we hypothesise this contributed to the generalizability of the study sample and high participant retention rate. Participants had severe respiratory impairment, with concomitant bulbar and physical impairment in many cases; representative of the general NMD population. Issues such as mobility, carer availability and respiratory compromise may be postulated to prevent participation, however anecdotally participants reported that the in-home visits balanced the burden of study involvement and enabled inclusion. We speculate that this element of the study design also contributed to over 96% of randomised

participants completing data collection at three-months, and strongly advocate future trials be designed with participants at the centre.

9.5 CONCLUSION

The results of this research project provide new insights into the efficacy of LVR therapy in people living with heterogeneous NMD. No previous research has comprehensively assessed the effect of LVR on respiratory and QoL outcomes in a controlled manner, and as such this body of work has made considerable contributions to the field. It has demonstrated that LVR is an easy and tolerated technique, able to be performed by almost all participants within a single session. Furthermore, the results of the pre-post intervention studies imbedded in this trial design suggest that regular therapy does not augment immediate effects. In fact, this research has corroborated existing data questioning the effect of a single LVR therapy session in people when they are medically-stable. The benefits of LVR and other assisted inflation techniques on airway clearance, alveolar ventilation and lung volumes during periods of acute respiratory compromise is one area identified for future research.

The RCT findings indicate that LVR can increase the maximal tolerable assisted inflation volume (i.e., LIC) over a three-month period, in the context of no demonstrable improvement in respiratory system physiology, respiratory symptoms or HRQoL. The process of measuring LIC incorporates a LVR manoeuvre in and of itself however, such that improvements observed after a short LVR session when participants were naïve to the technique likely reflect learning. The absence of effect on VC, static lung volumes and markers of respiratory muscle strength, in conjunction with no discernible dose-response and a statistically significant association between the improvement in LIC and change in peak pressure at LIC over the study period, imply that regular LVR may acclimatise people to tolerate higher pressures. It is also possible that a larger learning effect in the intervention group by chance contributed to the isolated increase in the primary outcome of LIC. However given the observed improvement in C_{rs} over time, predominantly in the LVR group, we can not rule out the possibility that regular LVR may improve underlying respiratory mechanics, especially if conducted for a longer duration. Long-term prospective studies are required to investigate factors such as when to initiate regular LVR, optimal dose, the length of time needed before

physiological changes are observed if they occur, and the longer-term impact of performing regular therapy on HRQoL and carer burden.

Lung insufflation capacity was selected as the primary outcome for this RCT as it quantifies the magnitude of assisted inflation possible in response to a therapy that aims to augment volume. Observational, retrospective studies have proposed that by improving LIC, respiratory function decline is ameliorated in the context of progressive disease. No prospective data exist to confirm this hypothesis however, and based on this work LIC would not appear to reflect respiratory system "range of motion". In the context of progressive NMDs, many of which are long-standing, a longer period of time may also be required to demonstrate a carry-over effect of increasing LIC to clinical outcomes. Further longitudinal studies evaluating serial respiratory and cough measures, incidence of RTI, patient-reported outcome measures including voice, ability to cough and clear secretions are much needed to inform clinical decision making.

Notwithstanding the breadth of future work required, the improvement in the primary outcome of LIC in the absence of apparent harm or burden, provides robust preliminary data supporting clinical recommendations and practice that regular LVR be performed by people living with NMD. The clinical significance of a higher LIC is still to be fully realised, but we have been able to demonstrate an effect that is compatible with the clinical and biologically-plausible rationale for this therapy. This research project contributes much-needed, crucial science to strengthen the evidence-base for care recommendations and hopefully improve knowledge, access, resources and ultimately outcomes for people living with progressive NMDs.

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11 Appendix

11.1 METHODS

11.1.1 DATA SAMPLING METHODS: CUSTOM-WRITTEN SCRIPT

Real-time processing of airflow sampled with the Hans Rudolph™ pneumotachometer occurred, to i) convert sampled airflow to BTPS conditions and ii) derive a volume signal. This was performed by constructing a custom-written script within the data acquisition software (Spike7) which was executed during testing. The first script component applied temperature and water vapour corrections to the inspiratory airflow, to convert to BTPS conditions. This BTPS-correction factor accounts for differences in test conditions which effect the volume of gas measured between a) calibration via syringe and b) participant inspiration and expiration.

The second component used the flow signal to determine volume. Based on Equation 11-1, volume can be calculated by multiplying flow by time for any single time point. To calculate the volume of air over a continuous measure of time, mathematical integration can be employed (Equation 11-2).

$$\dot{V} = \frac{V}{t}$$

$$where\ \dot{V} = flow, V = volume, t = time$$

$$Rearranging:$$

$$V = \dot{V} \cdot t$$

Equation 11-1

$$\boldsymbol{V} = (\boldsymbol{\dot{V}_1} \times \boldsymbol{t_1}) + (\boldsymbol{\dot{V}_2} \times \boldsymbol{t_2}) + (\boldsymbol{\dot{V}_3} \times \boldsymbol{t_3})$$

$$or \quad \boldsymbol{V} = \Delta t\ (\boldsymbol{\dot{V}_1} + \boldsymbol{\dot{V}_2} + \boldsymbol{\dot{V}_3})$$

$$where\ \Delta t\ is\ a\ constant\ period\ of\ time$$

$$\boldsymbol{V} = \int \dot{V} \cdot \Delta t$$

Equation 11-2

Data were sampled at 100 Hz therefore Δt = 0.01 seconds

11.1.2 PRINCIPLES UNDERLYING THE BTPS-CORRECTION FACTOR

The relationship between pressure, volume and temperature of a gas was first noted in the 17th Century by thermodynamic physicists. The Ideal Gas Law (Equation 11-3), stated in 1834, combined the laws of Boyle, Mariotte, Charles, Gay-Lussac and Avogadro to describe the behaviour of many gases under various conditions.

$$PV = nRT$$

$$V = \frac{nRT}{P}$$

Equation 11-3: Ideal Gas Law

where V = volume, n = amount of substance in gas (moles), R = gas constant, T = absolute temperature measured in kelvins, P = pressure

From this principle, it can be appreciated that the measured gas volume will increase as temperature increases and ambient pressure decreases. Ambient air enters the respiratory system and quickly reaches body temperature and is saturated with water vapour (BTPS conditions). When passing through a pneumotachometer, inspiratory flow is thus coming from ambient (ATP) conditions, whereas expiratory flow has been at BTPS conditions. Although the pneumotachometer measures both directions of airflow, a correction factor must be applied to account for the different conditions and hence correct volume. Furthermore, humidity of the gas will also affect the measured volume in addition to that predicted by applying the ideal gas law alone.

For the respiratory measurements performed in this study a heated pneumotachometer was necessary as participants both inspired and expired through the circuit, the latter gas being saturated with water vapour. To prevent condensation from forming on the internal mesh screens and altering the flow-resistance properties of the device, the pneumotachometer was heated to a temperature approximating that of expired air (i.e., 37°C). The calibration procedure was performed with the heater off, so that the pneumotachometer accurately measured the calibration volume from the syringe, with both at ATP conditions.

For expiratory measurements, the assumption was that the heated pneumotachometer maintained BTPS conditions, and hence no correction factor was required. This assumption was based on the following principles:

- barometric pressure is the same in both situations;
- temperature in the lungs is 37°C, drops to 34°C at the mouth and is heated back to 37°C by the pneumotachometer;
- difference in water vapour saturation of the gas in the lungs is negligible compared to when at the pneumotachometer. This assumption was assessed using the ratio of dry gas fraction (Equation 11-4), using mouth temperature as a conservative measure of temperature at the heated pneumotachometer:

$$\frac{\mathrm{Pb} - P_{\mathrm{H2O\ @\ 34C}}}{\mathrm{Pb} - P_{\mathrm{H2O\ @\ 37C}}}$$

Substituting these for the calculated values:

$$\frac{760 - 42}{760 - 47} = \frac{718}{713} = 1.007$$

Thus the saturation factor is less than 1% and hence can be ignored.

Equation 11-4: Ratio of dry gas

where $\boldsymbol{P_{\mathrm{H2O\ @\ 34C}}}$= water vapour saturation pressure at mouth temperature, $\boldsymbol{P_{\mathrm{H2O\ @\ 37C}}}$ = water vapour saturation pressure at body temperature

However, these same assumptions do not apply to the inspiratory airflow passing from ATP conditions, through the heated pneumotachometer. Given we wish to measure the *volume of air inspired into the lungs*, a correction factor must be applied to convert inspiratory flow measured at the pneumotachometer to BTPS conditions. Whilst the amount of gas in moles (n) will be the same, the volume will increase under BTPS conditions (Equation 11-5). Rearranging the ideal gas law:

$$PV = nRT$$

$$n = \frac{VP}{RT}$$

$$n_{Pn} = n_{BTPS}$$

$$\frac{V_{Pn}P}{RT_{Pn}} = \frac{V_{BTPS}P}{RT_{BTPS}}$$

$$V_{BTPS} = \frac{V_{Pn}T_{BTPS}}{T_{Pn}}$$

Equation 11-5: Effect of temperature on volume

where V_{BTPS} = actual volume of inspired air, V_{Pn} = measured volume at pneumotachometer, T_{BTPS} =body temperature (kelvins), T_{Pn} = temperature at pneumotachometer (kelvins)

Barometric pressure and the gas constant (R) will be the same under both conditions, however the heating effect of the pneumotachometer must be known; that is, whether it can heat the inspiratory flow from ambient room temperature to 37°C, across the various flow rates that will be encountered. The actual pneumotachometer temperature will also affect the amount of water vapour saturation and hence measured gas volume. The actual volume of inspired gas will therefore be comprised of a temperature correction and water vapour correction (Equation 11-6):

$$V_{BTPS} = V_{pn} . \frac{T_{BTPS}}{T_{Pn}} . \frac{\mathrm{Pb} - (\mathrm{RH\ x}\ P_{\mathrm{H2O\ @\ RT}})}{\mathrm{Pb} - P_{\mathrm{H2O\ @\ 37C}}}$$

Equation 11-6: Correction Factor for Inspired Volume

where V_{BTPS} = actual volume of inspired air, V_{Pn} = measured volume at pneumotachometer, T_{BTPS} =body temperature (kelvins), T_{Pn} = temperature at pneumotachometer (kelvins), $\mathbf{Pb}$ = barometric pressure (760mmHg), $\mathbf{RH}$ = room humidity, $\boldsymbol{P}_{\mathbf{H2O\ @\ RT}}$= partial pressure of water vapour saturated at ambient temperature, $\boldsymbol{P}_{\mathbf{H2O\ @\ 37C}}$ = water vapour saturation pressure at body temperature.

Room humidity and temperature can be measured using a whirling hydrogometer at the time of testing, and the partial pressure of water vapour for a given temperature can be approximated using the following equation (Equation 11-7):

$$P_{\mathrm{H2O}} = exp(20.386 - \frac{5132}{T})$$

Equation 11-7: Approximation of water vapour (P_{H2O})

where $\boldsymbol{T}$ = temperature in kelvins (273.15 + temperature °C)

In order to calculate the actual temperature of ambient air as it passes the pneumotachometer, a bench-test experiment was conducted (Section 11.1.3). The resultant correction factor equation was determined and programmed into the custom-written script used for respiratory function measurements in this research project (Equation 11-8).

$$V_{BTPS} = V_{pn} \cdot \frac{(273.15 + 37.0)}{(273.15 + (AT + \Delta T)} \cdot \frac{760 - (\mathrm{RH\ x}\ P_{\mathrm{H2O\ @\ RT}})}{760 - 47}$$

$$where\ P_{\mathrm{H2O@RT}} = exp(20.386 - \frac{5132}{273.15 + AT})$$

$$and\ AT = \text{ambient temperture measured in °C}, \Delta T = 5°\mathrm{C}$$

Equation 11-8: Final correction factor for converting inspiratory flow measurements to BTPS conditions

11.1.3 EXPERIMENT – HEATING CAPACITY OF PNEUMOTACHOMETER

11.1.3.1 BACKGROUND AND AIM

The temperature of inspired gas passing through a pneumotachometer must be known in order to calculate the temperature correction component of a BTPS-correction factor. Therefore the aims of this experiment were to: i) calculate the temperature of air passing through the pneumotachometer under various conditions, and ii) determine the necessary temperature correction factor if the pneumotachometer was unable to heat inspiratory gas flow from ambient temperature to 37°C.

11.1.3.2 METHOD

A sequence of 36 strokes of a known volume syringe (3L), at flow rates covering anticipated participant inspiratory and expiratory airflow (0.37-4.55 L/s) were sampled via the calibrated pneumotachometer under two test conditions: heater off (Condition 1) and heater on (set at 37°C) (Condition 2). Stroke volumes recorded by the pneumotachometer were measured from the volume signal.

Room air ambient temperature was measured using a whirling hygrometer (Sling Psychrometer, product code IC736700, instrumentchoice.com.au) at the time of testing. The experiment was conducted twice on the same day at the same ambient temperature, and repeated at two other ambient temperatures selected to represent anticipated study testing conditions:

1. 24°C
2. 24°C
3. 28°C
4. 18°C

Assuming the amount of gas (moles) passing from the syringe (ATP conditions) across the pneumotachometer under the varying conditions is constant, the ideal gas equation can be used to calculate the actual temperature of the heated pneumotachometer (Equation 11-9):

$$n = \frac{VP}{RT}$$

$$n_1 = n_2$$

$$\frac{V_1 P}{RT_1} = \frac{V_2 P}{RT_2}$$

$$T_2 = \frac{V_2}{V_1} \times T_1$$

Equation 11-9: Heated pneumotachometer temperature

where V_1 = volume measured heater off, T_1 = temperature heater off (ambient temperature, kelvins), V_2 = volume measured heater on, T_2 = temperature heater on (kelvins) = $\boldsymbol{T_1 + \Delta T}$

11.1.3.3 RESULTS

Stroke volumes were calculated from the volume signal for each individual syringe stroke, for each of the four trials. Mean volumes are presented in Table 11-1.

Solving for T_2 using the equation above, the temperature of inspiratory air as it passed through the pneumotachometer was calculated. The difference between ambient temperature (T_1) and the calculated temperature at the pneumotachometer (T_2) was defined as the heating capacity of the heater (ΔT).

Trial	Heater off T_1 = ambient temperature		Heater on (37 °C) T_2 = temperature unknown		ΔT ($T_2 - T_1$)	Calculated V_C if ΔT = 5 °C
	V_1 (L)	T_1	V_2 (L)	T_2 calculated		
1	2.994	24 °C = 297.15 K	3.046	302.25 K = 29 °C	5 °C	3.046
2	2.976	24 °C = 297.15 K	3.033	302.83 K = 30 °C	6 °C	3.027
3	2.976	28 °C = 301.15 K	3.012	304.85 K = 32 °C	4 °C	3.025
4	2.939	18 °C = 291.15 K	2.978	295.09 K = 22 °C	4 °C	2.989
				Mean heating capacity	4.61 °C	

Table 11-1: Mean volume of 36 strokes delivered with a 3-litre (L) syringe, measured by pneumotachometer with heater off (V_1) and heater on (V_2), at varying room temperatures (Trials 1 – 4)

Where T_1 = temperature at the pneumotachometer (mirroring ambient temperature), T_2 = temperature at the pneumotachometer when heater set to 37°C (actual pneumotachometer temperature unknown but calculated using the ideal gas equation).
Heating capacity (ΔT) was defined as the magnitude by which the heater warmed ambient inspiratory airflow. Assuming a ΔT of 5°C, corrected volume (V_c) was calculated (shaded cells).

Although the heater was set to 37°C, it failed to heat inspired gas from ambient room temperature to body temperature (37°C) (see calculated T_2 values in Table 11-1). The mean heating capacity of the pneumotachometer was 4.6 °C, hence the temperature of inspiratory air as it passed by the pneumotachometer was approximated to equal ambient temperature + a standard heating capacity of 5°C.

To determine the degree of error introduced into volume calculations if this standard heating capacity of 5°C was used as the temperature correction component of the BTPS-correction factor, the corrected volume (V_C) was calculated for trials within this experiment and compared to that measured (V_2) (see shaded cells in Table 11-1). A mean absolute error range of -6 mL to +13 mL was observed over the trials (representing delivered volume ± 0.43%).

11.1.3.4 CONCLUSION

Measuring the volume of air inspired via a pneumotachometer assumes that the airflow passing from the ambient atmosphere through the sensor is heated to body temperature. If the heater is unable to warm ambient air to 37°C, the measured volume will be less than the inspired volume, due to the behaviour of gas under different conditions. By knowing the temperature under which the sensor is sampling airflow, a correction factor can be computed to convert the volume of gas measured by the pneumotachometer (V_{Pn}) to the volume of gas inspired (V_{BTPS}) to account for the expansion of gas that will occur within the respiratory system (Equation 11-10).

$$V_{BTPS} = \frac{V_{Pn} T_{BTPS}}{T_{Pn}}$$

Equation 11-10

On a setting of 37°C, the heated pneumotachometer used for this research study did not heat ambient air, sampled across flow rates anticipated in the population of participants with NMD, to body temperature. The experiment conducted demonstrated that the temperature of gas measured by the pneumotachometer could be approximated by adding a value of 5°C to the ambient temperature.

11.1.4 EXCEL MACRO FOR ANALYSIS OF LVR COUNTER DATA

To aid analysis of LVR usage data, an Excel macro converted the raw data output into summary information. This macro was based on an existing macro created for analysing state-change data from a separate research project, conducted by the current research team. The macro applied an algorithm to the raw output of naughts and ones, grouping these events into a bout of activity or "session". The resultant summary data consisted of date, session start time, session end time, session duration (hh:mm:ss) and number of state changes counted within a session.

Use of LVR therapy was assessed by: i) the number of sessions performed per day, and ii) total session duration per day. The macro defined a session as the presence of compressions (i.e., more than one state change) occurring for a minimum of 15 seconds (Table 11-2). This value was selected based on the smallest session dose reported in the available literature. Rafiq and colleagues prescribed "2-3 cycles of breath-stacking per session, stacking 3-5 breaths per cycle", which could be interpreted as 2-3 repetitions of maximal insufflation breaths per session, each comprising 3-5 compressions.[105] This could conceivably be performed in approximately 15 seconds if participants required minimal rest between repetitions. Although the dosage prescribed in this study was greater than this, aligning *minimum LVR usage* with the published literature would allow comparison of our findings to existing work. In other words, if participants performed LVR for 15 seconds duration, this would count as an intervention session as defined by other researchers, despite being less than that prescribed here.

Lung volume recruitment use was also assessed according to session duration, providing a marker for concordance with the LVR prescription used in this RCT. The macro did not set an upper limit of session duration in its interpretation of the raw output as individual participants may take varying time to perform LVR, however if more than 60 minutes separated two state changes, this was arbitrarily interpreted as two separate LVR sessions (Table 11-2).

Macro label	Macro setting	Function
Minimum session length (minute)	0.25	Minimum time required to be counted as a "session"
Maximum time without compression in session (minutes)	60	Time period separating sessions
Start time	00:00:00 hours	Commence "day" period
End time	23:59:59 hours	End "day" period

Table 11-2: Macro parameters

Two rounds of macro testing occurred to ensure that the automated process interpreted the state changes correctly. The first test used the data from the three sampling rate tests. For the second test, the first and last week of usage recorded by the first participant randomised to LVR was employed. For both these scenarios, an unblinded assessor compared the summary information generated by the macro in Excel to their raw Omega® output. In both cases, the summary variables of LVR usage (i.e., number of sessions per day recorded, total session duration per day) were identical, regardless of method used to derive them.

11.2 C_{RS} SIGNAL ANALYSIS: SCORER RELIABLITY

Scorer	Participant	Session 1 C_{rs} summary value	Session 2 C_{rs} summary value	Session 3 C_{rs} summary value	Intra-rater ICC
A	1	0.0499	0.0506	0.0508	>0.99
	2	0.0192	0.0191	0.0195	(>0.99, >0.99)
	3	0.0096	0.0096	0.0095	***p*<0.0001**
B	1	0.0413	0.0392	0.0510	0.98
	2	0.0184	0.0182	0.0192	(0.90, >0.99)
	3	0.0097	0.0092	0.0094	***P*=0.001**
C	1	0.0490	0.0441	0.0411	0.99
	2	0.0185	0.0186	0.0181	(0.96, >0.99)
	3	0.0094	0.0095	0.0095	***p*<0.0001**
Inter-rater ICC		0.99 (0.95, >0.99) ***p*<0.001**	0.99 (0.92, >0.99) ***p*<0.001**	0.99 (0.93, >0.99) ***p*<0.001**	

Table 11-3: Inter- and intra-rater reliability of scorers

Total respiratory system compliance (C_{rs}) summary value (L/cmH_2O) calculated for each participant, on each scoring session, by each scorer. The summary value represents the mean of all acceptable traces in that test session. Order of participants was randomised within each scoring session. Inter-rater intraclass correlation coefficient (ICC) estimates (95% confidence interval) based on mean ratings, two-way random-effects model with absolute agreement. Intra-rater intraclass correlation coefficient (ICC) estimates (95% confidence interval) based on mean ratings, two-way mixed-effects model. *P*-value <0.05 considered statistically significant (in **bold**).

11.3 BASELINE CHARACTERISTICS

11.3.1 BASELINE RESPIRATORY FUNCTION BY PARTICIPANT

This research trial recruited participants with NMD and respiratory system involvement, defined as a FVC <80% predicted normal. However, since study design the Global Lung Initiative (GLI) introduced recommendations that spirometric values be classified relative to lower limit of normal (LLN) values. The following table demonstrates that five participants (ID# 7, #50, #62, #67 and #80) had FVC values at study entry that were greater than the LLN.

Forced vital capacity was selected as the inclusion criterion as this is measured routinely at clinical review and was therefore an available screen of potential participants. However, as per Section xxx, slow vital capacity (SVC) was measured throughout this study. No statistically significant difference was found between screening FVC (prior to study entry) and SVC (at study baseline, Timepoint 0a) (Student's paired *t*-test, p=0.92).

ID	FVC (L)	FVC (% pred)	FVC LLN	FVC Z score	< LLN	SVC (L)
1	1.670	62.3	1.97	-2.37	Y	1.456
2	0.430	13.6	2.49	-7.42	Y	0.428
3	0.280	8.5	2.62	-8.46	Y	0.255
4	2.710	66.8	2.98	-2.06	Y	2.183
5	2.190	53.3	3.05	-3.00	Y	2.140
6	1.240	44.6	2.05	-3.59	Y	1.178
7	3.110	73.7	3.11	-1.64	N	3.340
8	NA					0.717
9	NA					1.200
10	2.070	38.5	4.16	-4.57	Y	2.338
11	2.460	49.1	3.82	-3.55	Y	2.580
12	4.080	73.6	4.47	-2.24	Y	3.667

ID	FVC (L)	FVC (% pred)	FVC LLN	FVC Z score	< LLN	SVC (L)
13	0.910	16.1	4.57	-7.38	Y	0.545
14	1.790	52.5	2.55	-3.12	Y	2.055
15	1.230	35.9	2.55	-4.18	Y	1.266
16	2.400	38.0	5.12	-5.47	Y	2.273
17	1.500	36.9	3.25	-5.42	Y	1.643
18	0.860	17.3	4.03	-7.38	Y	0.891
19	0.740	15.3	3.87	-7.15	Y	0.828
20	0.740	30.3	1.95	-6.13	Y	0.704
21	1.560	35.7	3.18	-3.96	Y	1.710
22	1.120	39.5	2.14	-4.29	Y	1.124
23	0.700	29.4	1.92	-6.11	Y	0.818
24	0.570	21.0	2.17	-7.06	Y	0.653
25	2.680	65.3	3.03	-2.20	Y	2.526
26	0.750	17.5	3.29	-6.03	Y	0.737
27	0.740	21.9	2.60	-5.99	Y	0.553
28	0.590	30.7	1.54	-6.09	Y	0.718
29	1.380	41.9	2.39	-3.61	Y	1.769
30	1.350	46.3	2.22	-3.76	Y	1.313
31	1.450	32.5	3.34	-4.46	Y	1.652
32	2.180	60.6	2.62	-2.40	Y	2.405
33	1.960	49.9	2.84	-3.00	Y	2.108
34	0.570	27.2	1.54	-4.82	Y	0.688
35	1.240	42.7	2.21	-4.10	Y	1.362
36	0.680	24.7	2.20	-6.68	Y	0.737
37	1.900	43.5	3.46	-4.54	Y	1.794
38	1.930	56.6	2.61	-3.12	Y	1.913
39	0.490	17.1	2.22	-6.61	Y	0.452

ID	FVC (L)	FVC (% pred)	FVC LLN	FVC Z score	< LLN	SVC (L)
40	0.650	28.0	1.84	-6.07	Y	0.672
41	0.400	14.6	2.15	-7.24	Y	0.430
42	2.580	66.6	2.75	-1.90	Y	2.810
43	0.610	23.8	2.07	-7.17	Y	0.630
44	2.810	64.1	3.27	-2.33	Y	2.815
45	1.450	46.2	2.37	-3.73	Y	1.624
46	2.360	54.3	3.28	-3.10	Y	1.697
47	1.950	46.1	3.43	-4.75	Y	1.947
48	1.060	34.5	2.46	-5.72	Y	1.016
49	1.740	51.4	2.71	-4.16	Y	1.631
50	3.620	76.4	3.57	-1.58	N	1.524
51	2.840	63.4	3.36	-2.43	Y	2.674
52	0.280	8.2	2.73	-8.51	Y	0.312
53	2.060	38.2	4.23	-4.78	Y	2.232
54	0.480	15.0	2.55	-7.63	Y	0.467
55	2.230	61.7	2.62	-2.30	Y	2.322
56	2.010	46.2	3.25	-3.54	Y	2.099
57	0.780	16.4	3.78	-6.88	Y	0.871
58	1.490	37.2	3.25	-5.56	Y	1.476
59	2.260	59.8	2.84	-2.68	Y	2.347
60	1.720	37.8	3.66	-5.30	Y	2.184
61	1.130	34.0	2.48	-4.48	Y	1.198
62	3.660	77.6	3.55	-1.49	N	3.592
63	2.420	55.1	3.26	-2.89	Y	2.560
64	1.450	31.0	3.62	-5.13	Y	1.552
65	1.470	26.0	4.56	-6.45	Y	1.394
66	0.720	23.6	2.29	-5.42	Y	0.872

ID	FVC (L)	FVC (% pred)	FVC LLN	FVC Z score	< LLN	SVC (L)
67	3.170	79.1	2.94	-1.29	N	3.145
68	1.110	30.2	2.94	-6.11	Y	1.264
69	1.060	34.3	2.34	-4.71	Y	0.910
70	2.280	72.9	2.31	-1.71	Y	2.108
71	1.480	39.9	2.91	-4.83	Y	1.585
72	1.910	62.5	2.24	-2.33	Y	2.015
73	2.540	57.1	3.32	-2.79	Y	2.601
74	1.000	37.7	1.98	-4.25	Y	1.157
75	0.800	22.3	2.82	-6.43	Y	0.692
76	1.120	42.6	1.95	-3.79	Y	1.273
77	0.470	15.7	2.40	-7.72	Y	0.549
78	1.660	34.0	3.71	-4.57	Y	1.553
79	3.010	57.0	4.04	-3.02	Y	3.757
80	1.970	73.6	1.89	-1.47	N	1.972

Table 11-4: Individual participant data illustrating screen forced vital capacity (FVC, litres), corresponding % predicted normal (% pred), lower limit of normal (LLN)[244] and Z-score. Slow vital capacity (SVC, litres) at study baseline (Timepoint 0a) is provided for comparison (Student's paired *t*-test p=0.92)

Five participants (ID # 7, 50, 62, 67 and 80) had FVC <80% predicted but greater than LLN at study screening.

11.3.2 SELECTED RESPIRATORY VARIABLES, BY DISEASE TYPE

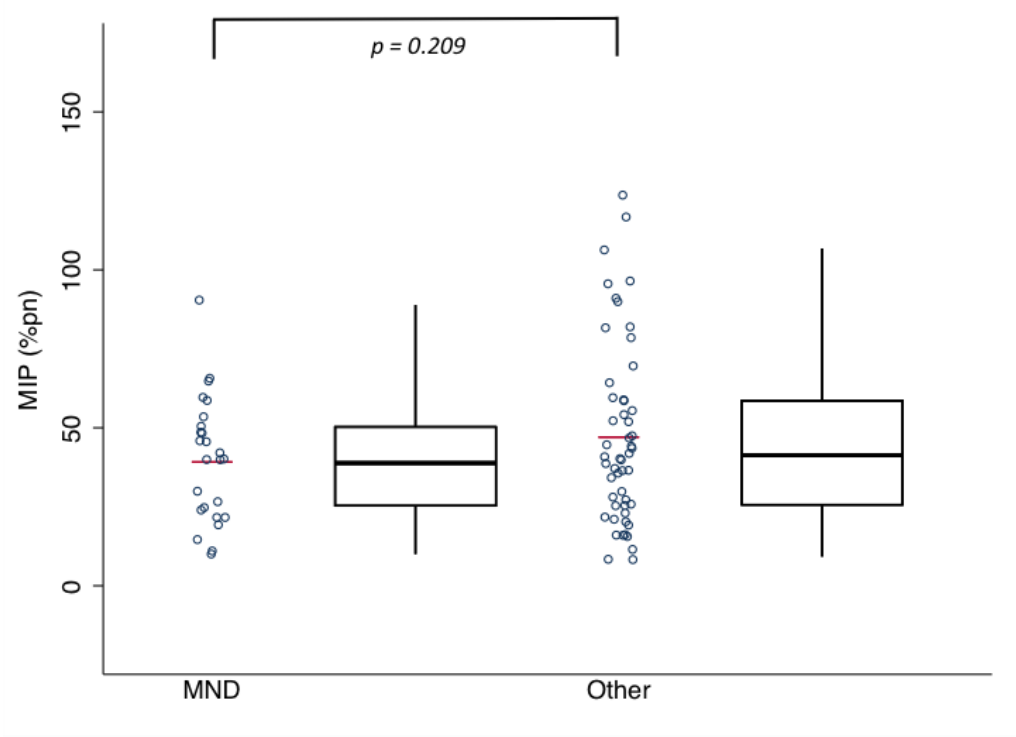

Figure 11-1: Maximal inspiratory pressure (MIP, % of predicted normal) in people with MND and Other NMDs, at Timepoint 0a

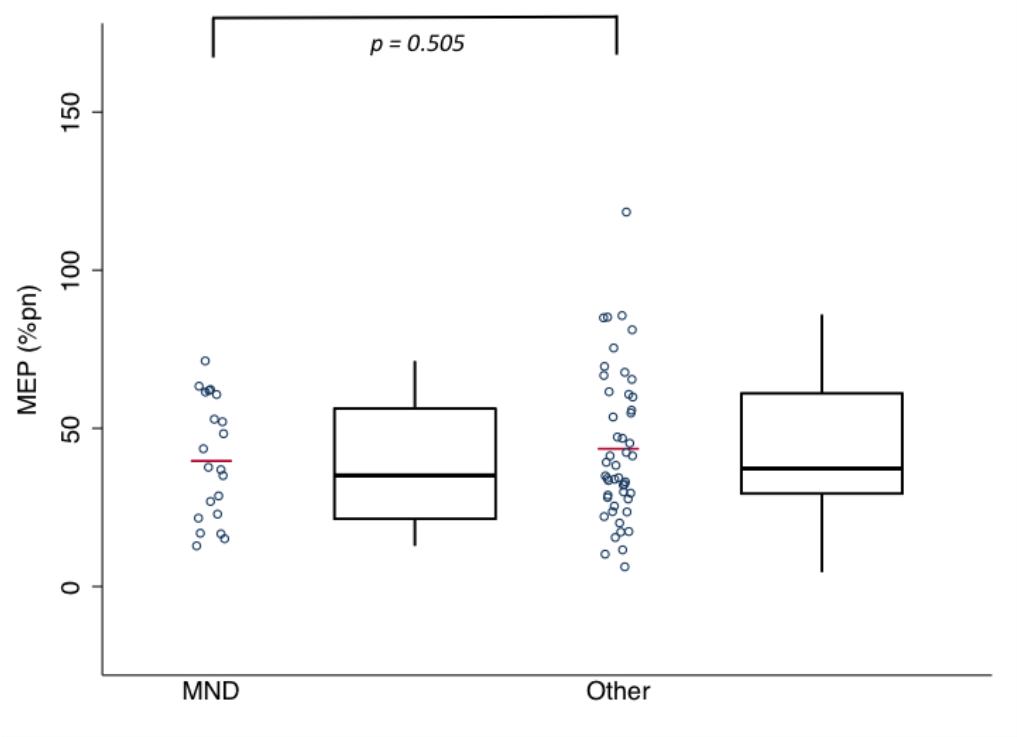

Figure 11-2: Maximal expiratory pressure (MEP, % of predicted normal) in people with MND and Other NMDs, at Timepoint 0a

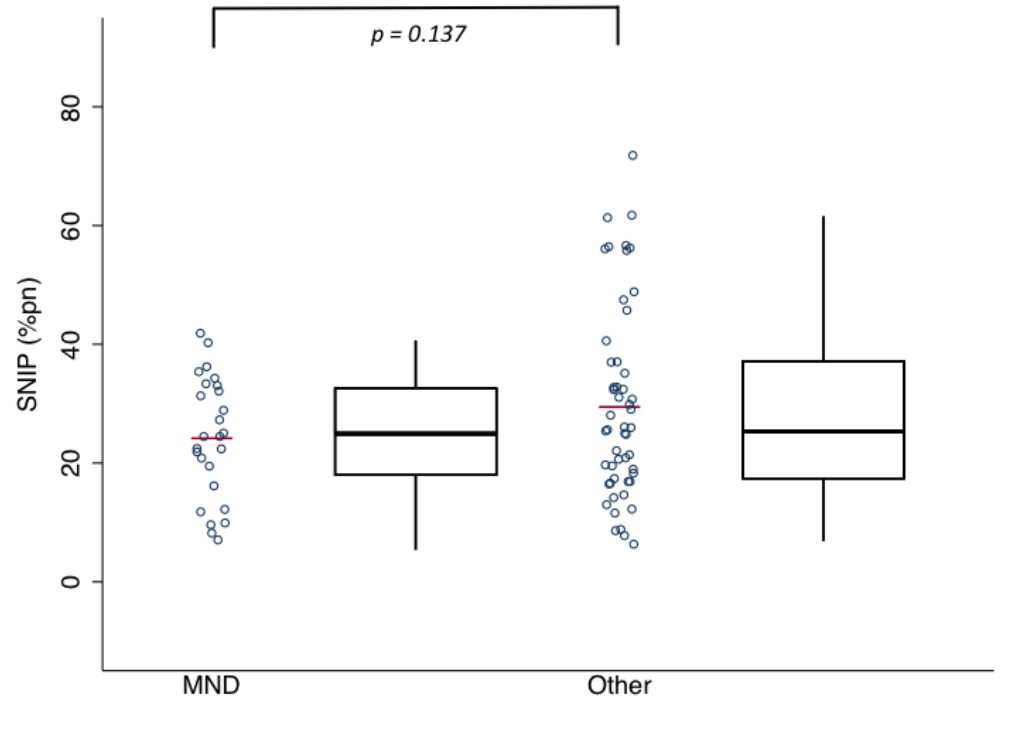

Figure 11-3: Sniff nasal inspiratory pressure (SNIP, % of predicted normal) in people with MND and Other NMDs, at Timepoint 0a

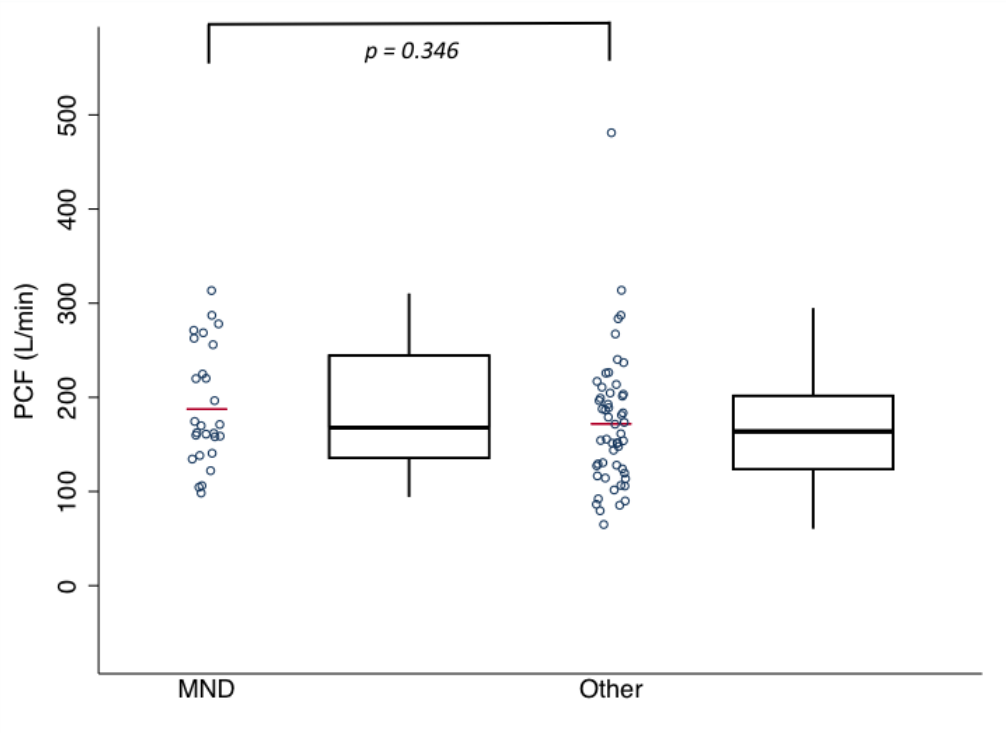

Figure 11-4: Unassisted peak cough flow (PCF, litres per minute) in people with MND and Other NMDs, at Timepoint 0a

11.3.3 MULTIVARIATE REGRESSION MODELS FOR VC AND PCF

Regression models were built manually for each disease type for the response variables VC and PCF, using explanatory variables that were found to be significant on univariate analysis.

11.3.3.1 MULTIVARIATE REGRESSION FOR VC IN MND

Response Variable	Explanatory Variables – MND				Adj R^2	*p*-value	RMSE
VC L	**Height**				0.44	0.0001	0.56
VC	**C_{rs}**				0.20	0.012	0.67
VC	**Height**	**C_{rs}**			0.49	0.0001	0.53
VC	**MIP**				0.33	0.002	0.63
VC	**Height**	**MIP**			0.60	<0.0001	0.49
VC	**Height**	**MIP**	C_{rs}	*Keep height, MIP*	0.60	<0.0001	0.48
VC	**MEP**				0.33	0.004	0.54
VC	**Height**	MIP	**MEP**	*Keep height, MEP*	0.69	**0.0001**	0.37

Table 11-5: Multivariate regression build for VC (L) in people with MND

Bold variables indicate statistically significiant within model.

Response Variable	Explanatory Variables – MND			Adj R^2	*p*-value	RMSE
VC %	Height			0.01	0.276	15.29
VC	**C_{rs}**			0.14	0.029	14.20
VC	**MIP**			0.21	0.012	13.59
VC	**MEP**			0.29	0.007	11.22
VC	**MEP**	C_{rs}	*Keep MEP*	0.27	0.024	11.41
VC	**MIP**	C_{rs}	*Keep MIP*	0.24	0.019	13.36
VC	**MEP**	**MIP**	*Keep MIP and MEP*	0.37	0.008	10.78

Table 11-6: Multivariate regression build for VC in people with MND – using % predicted VC, which normalises the absolute VC for individual height, age, sex

Bold variables indicate statistically significiant within model.
Note that Height dropped out of the regression model.

11.3.3.2 MULTIVARIATE REGRESSION FOR VC IN OTHER NMD

Response Variable	Explanatory Variables – Other NMD			Adj R^2	*p*-value	RMSE
VC L	**Age**			0.13	0.005	0.72
VC	**Height**			0.37	<0.0001	0.62
VC	**Weight**			0.27	<0.0001	0.66
VC	**Height**	Weight	*Keep height, drop weight*	0.38	<0.0001	0.61
VC	**Height**	Age	*Keep height, drop age*	0.39	<0.0001	0.61
VC	MIP			0.04	0.091	0.76
VC	MEP			0.03	0.128	0.78
VC	**C_{rs}**			0.27	<0.0001	0.64
VC	**Height**	**C_{rs}**	*Keep C_{rs}, height*	0.36	**<0.0001**	0.60

Table 11-7: Multivariate regression build for VC in people with other NMDs

Bold variables indicate statistically significiant within model.

Response Variable	Explanatory Variables – Other NMD				Adj R^2	*p*-value	RMSE
VC %	**Age**				0.27	0.0001	15.00
VC	**Height**				0.07	0.031	16.85
VC	Height	**Age**		*Keep age*	0.26	0.0003	15.06
VC	**C_{rs}**				0.13	0.006	15.92
VC	**Age**	**C_{rs}**		*Keep age, C_{rs}*	0.27	0.0003	14.65
VC	**Age**	**C_{rs}**	Height	*Keep age, C_{rs}*	0.30	0.0010	14.78

Table 11-8: Multivariate regression build for VC in people with other NMDs – using % predicted VC, which normalises the absolute VC for individual height, age, sex

Bold variables indicate statistically significiant within model.

Note that Height dropped out of the regression model, however age did not.

11.3.3.3 MULTIVARIATE REGRESSION FOR PCF IN MND

Response Variable	Explanatory Variables – MND			Adj R^2	*p*-value	RMSE
PCF	**Height**			0.29	0.002	51.6
PCF	**VC**			0.43	0.0001	46.4
PCF	**IC**			0.44	0.001	49.5
PCF	**ERV**			0.30	0.009	55.2
PCF	**IC**	ERV	*Keep IC*	0.48	0.002	47.4
PCF	**IC**	Height	*Keep IC*	0.45	0.003	48.8
PCF	**MEP**			0.32	0.004	52.2
PCF	**MIP**			0.27	0.005	54.3
PCF	IC	MEP		0.32	0.031	54.3
PCF	**IC**	MIP	*Keep IC*	0.46	0.004	50.0
PCF	**C_{rs}**			0.24	0.006	53.5
PCF	**IC**	C_{rs}	*Keep IC*	0.48	0.002	47.5

Table 11-9: Multivariate regression build for PCF in people with MND

Bold variables indicate statistically significiant within model.

11.3.3.4 MULTIVARIATE REGRESSION FOR PCF IN OTHER NMD

Response Variable	Explanatory Variables – Other NMD			Adj R^2	*p*-value	RMSE
PCF	**Age**			0.10	0.016	70.5
PCF	**Height**			0.09	0.020	70.8
PCF	**Weight**			0.21	0.0005	66.0
PCF	**VC**			0.40	<0.0001	57.5
PCF	**IC**		*Keep VC*	0.38	<0.0001	60.9
PCF	**ERV**		*Keep VC*	0.10	0.024	73.5
PCF	**C_{rs}**			0.12	0.011	54.4
PCF	**MEP**			0.16	0.004	67.9
PCF	**VC**	**MEP**	*Keep VC, MEP*	0.43	<0.0001	55.8
PCF	**VC**	C_{rs}	*Keep VC*	0.49	<0.0001	40.7
PCF	**VC**	**MEP** C_{rs}	*C_{rs} not signif in model*	0.49	<0.0001	39.5

Table 11-10: Multivariate regression for PCF in people with other NMDs

Bold variables indicate statistically significiant within model.

11.3.4 LOGISTIC REGRESSION MODEL FOR RESPIRATORY TRACT INFECTIONS

The manual build up of the logistic regression model to investigate factors associated with a past episode of RTI is presented below.

Response Variable	Explanatory Variables				Log likelihood	LR chi^2	*p*-value
RTI	**Disease**				-50.9	7.19	0.007
RTI	Age				-52.9	3.33	0.068
RTI	**VC**				-52.3	4.44	0.035
RTI	VC	**Disease**		*Keep disease*	-50.2	7.55	0.023
RTI	**PCF**				-51.1	5.83	0.016
RTI	**PCF**	**Disease**			-48.2	11.55	0.003
RTI	**PCF**	**Disease**	VC	*Keep PCF, disease Drop VC*	-48.0	12.06	0.007
RTI	MIP				-51.9	0.77	0.380
RTI	MEP				-47.0	0.03	0.861
RTI	C_{rs}				-48.5	0.36	0.547
RTI	IC				-41.9	3.05	0.081
RTI	ERV				-42.7	1.49	0.222
RTI	**TLC**			*Keep RV: FRC = RV + ERV, but ERV by itself is not significant. Similarly with IC, ERV and TLC.*	-40.7	5.55	0.018
RTI	**FRC**				-40.8	5.40	0.020
RTI	**RV**				-40.2	6.61	0.010
RTI	**PCF**	**Disease**	RV	*Keep PCF, disease Model without RV stronger*	-38.0	11.04	0.012

Table 11-11: Logistic regression model for factors associated with past history of respiratory tract infection (RTI) in people with neuromuscular disease (NMD)

11.3.5 LVR-Based Respiratory Variables, By Disease Type

Individual participant data, grouped by disease type for sub-group comparisons, is graphed along with the corresponding box plots, for each of the LVR-based respiratory function outcome measures at study baseline (Timepoint 0a).

Where: MND = motor neurone disease; Other = other neuromuscular diseases. Hollow circles represent individual participant data, red marker indicates sub-group mean. Box plot represents median, upper and lower quartiles; whiskers represent data within 1.5x IQR of these quartiles. *P*-value refers to Student's independent two-sample *t*-test for comparison of means.

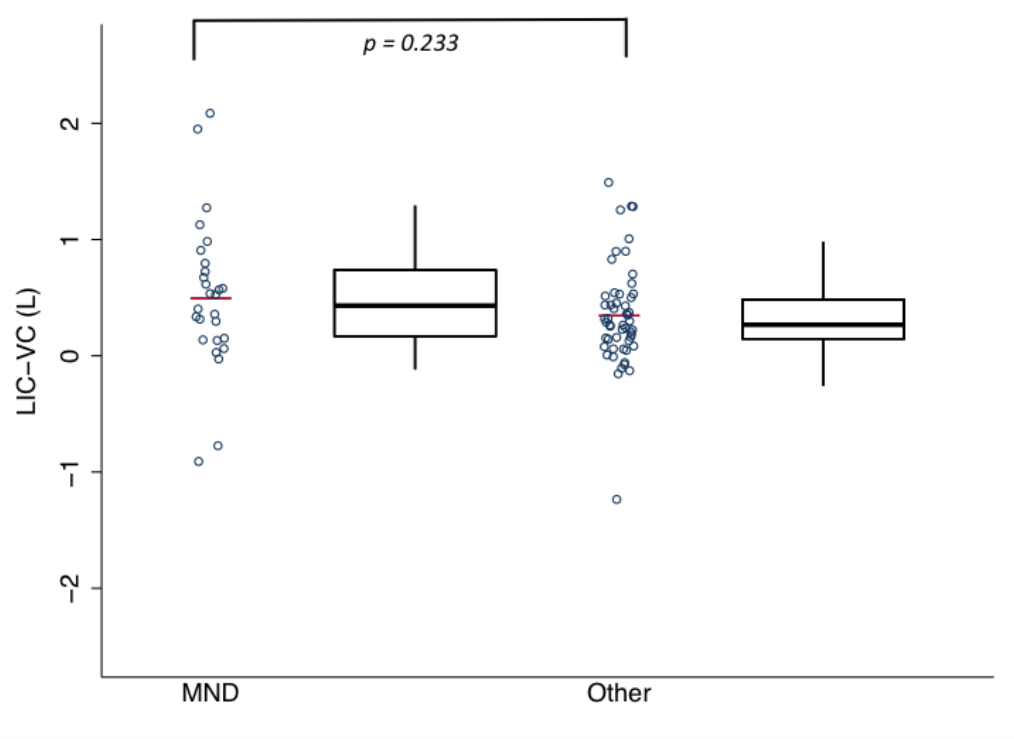

Figure 11-5: Lung insufflation capacity minus vital capacity difference (LIC-VC, litres) in people with MND and Other NMDs, at Timepoint 0a

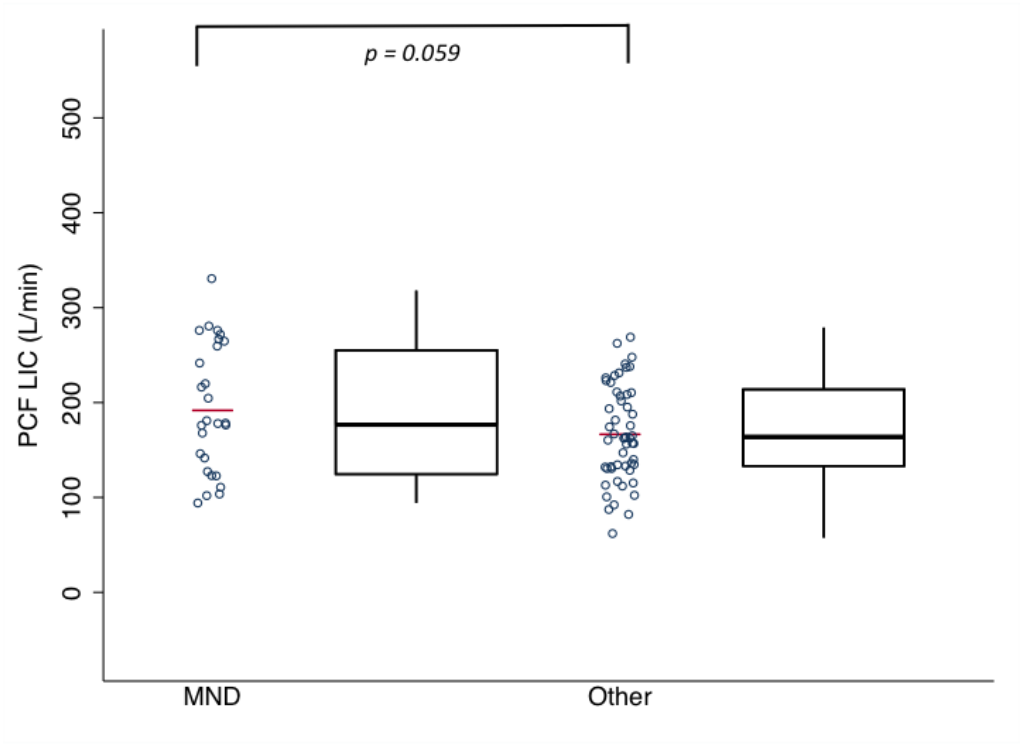

Figure 11-6: Peak cough flow from lung insufflation capacity ($PCF_{LIC,}$ litres per minute) in people with MND and Other NMDs, at Timepoint 0a

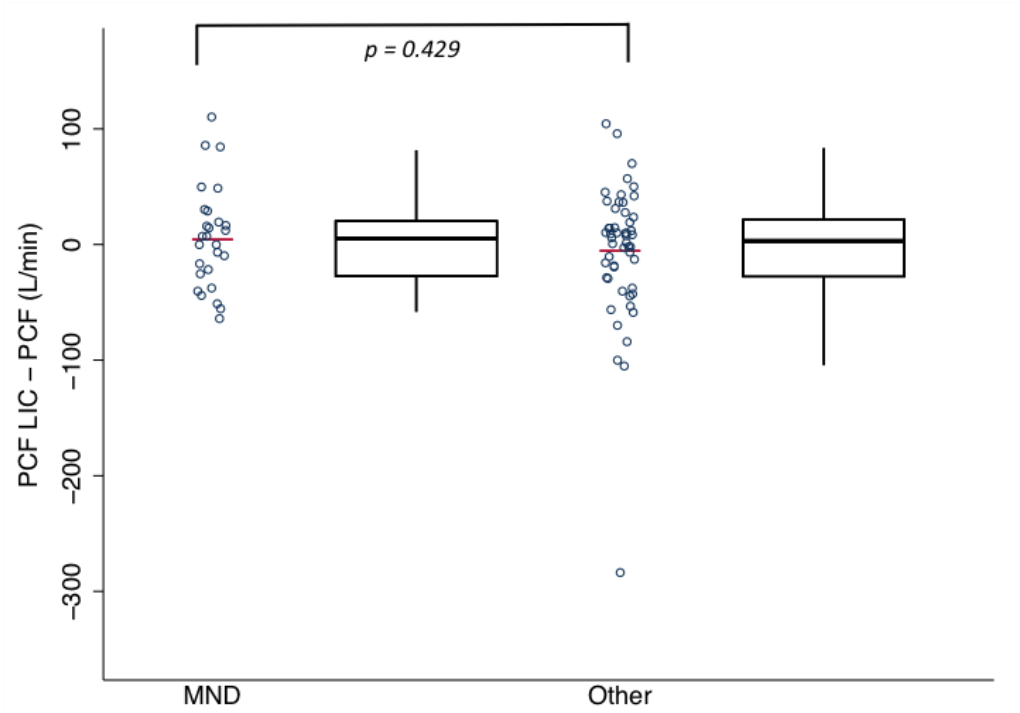

Figure 11-7: Peak cough flow from lung insufflation capacity minus unassisted peak cough flow (PCF_{LIC} – PCF, litres per minute) in people with MND and Other NMDs, at Timepoint 0a

11.4 IMMEDIATE EFFECTS OF LVR

11.4.1.1 WITHIN GROUP COMPARISON OF EFFECT OF LVR ON RESPIRATORY FUNCTION; BY DISEASE SUB-GROUPS

Variable		(n)	Timepoint 0a mean±SD	Timepoint 0b mean±SD	Δ at Time 0 Mean difference (95% CI)	*p*-value
LIC (L)	All	(78)	1.99 ± 1.02	2.12 ± 1.07	0.13 (0.05 – 0.21)	**0.002**
	MND	(26)	2.65 ± 1.06	2.81 ± 1.04	0.15 (-0.06 – 0.36)	0.151
	Other	(52)	1.66 ± 0.83	1.77 ± 0.92	0.12 (0.05 – 0.18)	**0.001**
VC (L)	All	(78)	1.57 ± 0.86	1.54 ± 0.84	-0.03 (-0.07 – 0.01)	0.142
	MND	(26)	2.14 ± 0.75	2.09 ± 0.77	-0.05 (-0.15 – 0.04)	0.250
	Other	(52)	1.28 ± 0.77	1.27 ± 0.74	-0.02 (-0.05 – 0.02)	0.377
LIC-VC (L)	All	(78)	0.42 ± 0.50	0.57 ± 0.43	0.16 (0.07 – 0.24)	**0.0003**
	MND	(26)	0.51 ± 0.67	0.72 ± 0.51	0.21 (0.00 – 0.41)	0.051
	Other	(52)	0.37 ± 0.39	0.51 ± 0.37	0.13 (0.06 – 0.21)	**0.001**
LIC-VC (%VC)	All	(78)	36.5 ± 45.9	45.9 ± 43.8	9.4 (2.9 – 15.8)	**0.005**
	MND	(26)	26.9 ± 32.6	37.9 ± 27.3	10.9 (0.3 – 21.6)	**0.045**
	Other	(52)	41.3 ± 50.8	49.9 ± 49.8	8.6 (0.3 – 16.8)	**0.043**
C_{rs} (L/cmH_2O)	All	(65)	0.0377 ± 0.0258	0.0415 ± 0.0270	0.0038 (0.0001 – 0.0075)	**0.047**
	MND	(19)	0.0501 ± 0.0252	0.0615 ± 0.0285	0.0115 (0.0014 – 0.0216)	**0.029**
	Other	(46)	0.0326 ± 0.0245	0.0332 ± 0.0032	0.0006 (-0.0025 – 0.0038)	0.688

Variable		(n)	Timepoint 0a mean±SD	Timepoint 0b mean±SD	Δ at Time 0 Mean difference (95% CI)	*p*-value
Specific C_{rs} ($L/cmH_2O/L$)	All	(44)	0.0316 ± 0.0174	0.0356 ± 0.0219	0.0041 (0.0011 – 0.0070)	**0.008**
	MND	(10)	0.0280 ± 0.0133	0.0306 ± 0.0146	0.0027 (-0.0002 – 0.0055)	0.065
	Other	(34)	0.0326 ± 0.0185	0.0371 ± 0.0236	0.0045 (0.0007 – 0.0082)	**0.021**
TLC (L)	All	(49)	2.64 ± 1.45	2.60 ± 1.41	-0.03 (-0.10 – 0.03)	0.266
	MND	(11)	3.99 ± 1.80	3.80 ± 1.67	-0.19 (-0.37– 0.00)	**0.049**
	Other	(38)	2.25 ± 1.07	2.25 ± 1.13	0.01 (-0.05 – 0.07)	0.763
FRC (L)	All	(49)	1.39 ± 0.98	1.36 ± 0.97	-0.03 (-0.09 – 0.03)	0.348
	MND	(11)	2.29 ± 1.32	2.14 ± 1.26	-0.16 (-0.32– 0.01)	0.057
	Other	(38)	1.12 ± 0.67	1.13 ± 0.74	0.01 (-0.06 – 0.07)	0.824
RV (L)	All	(49)	1.00 ± 0.73	0.99 ± 0.71	-0.02 (-0.07 – 0.04)	0.610
	MND	(11)	1.65 ± 0.88	1.51 ± 0.83	-0.14 (-0.33 – 0.06)	0.154
	Other	(38)	0.82 ± 0.57	0.84 ± 0.61	0.02 (-0.03 – 0.07)	0.469
IC (L)	All	(49)	1.24 ± 0.70	1.25 ± 0.67	0.00 (-0.04 – 0.04)	0.890
	MND	(11)	1.70 ± 0.70	1.67 ± 0.73	-0.03 (-0.17 – 0.11)	0.642
	Other	(38)	1.11 ± 0.65	1.13 ± 0.61	0.01 (-0.02 – 0.05)	0.501
ERV (L)	All	(49)	0.38 ± 0.32	0.37 ± 0.34	-0.01 (-0.05 – 0.02)	0.435
	MND	(11)	0.65 ± 0.49	0.63 ± 0.49	-0.02 (-0.13 – 0.09)	0.708
	Other	(38)	0.31 ± 0.21	0.29 ± 0.25	-0.01 (-0.05 – 0.02)	0.497
PCF (L/min)	All	(78)	175.5 ± 69.1	169.9 ± 57.6	-5.6 (-15.0 – 3.9)	0.244
	MND	(26)	185.1 ± 61.4	190.6 ± 66.4	5.4 (-6.4 – 17.3)	0.351
	Other	(52)	170.6 ± 72.8	159.7 ± 50.1	-11.1 (-23.9 – 1.8)	0.090

Variable		(n)	Timepoint 0a mean±SD	Timepoint 0b mean±SD	Δ at Time 0 Mean difference (95% CI)	*p*-value
PCF_{LIC} (L/min)	All	(77)	174.8 ± 56.7	186.4 ± 57.9	11.6 (3.7 – 19.5)	**0.005**
	MND	(26)	189.2 ± 65.3	195.9 ± 63.1	6.7 (-6.1 – 19.5)	0.293
	Other	(51)	167.4 ± 50.9	181.6 ± 55.0	14.1 (3.9 – 24.3)	**0.008**
PCF_{LIC} – PCF	All	(77)	-1.5 ± 51.9	15.7 ± 39.5	17.2 (4.2 – 30.2)	**0.010**
(L/min)	MND	(26)	4.1 ± 43.2	5.3 ± 37.9	1.2 (-14.3 – 16.8)	0.870
	Other	(51)	-4.3 ± 56.0	21.0 ± 39.6	25.3 (7.5 – 43.2)	**0.006**

Table 11-12: Pairwise comparisons of the immediate effect of LVR on respiratory function in people with NMD. All = whole cohort, MND = people with motor neurone disease, Other = people with other NMDs including restrictive chest wall disease. Total number of participants with MND = 27, total number of participants with Other NMDs = 53. P-value represents paired t-test comparison.

(n) = the number of participants with technically acceptable measurements at both timepoints. Results were not obtainable in all due to bulbar impairment, technical issues or fatigue. All variables except for PCF were significant at model level on linear mixed modelling. Shaded cells represent variables with statistically significant change on model *and* interaction effects (i.e., C_{rs}, TLC, FRC and RV). Main effects of time were noted for C_{rs}, specific C_{rs}, LIC, LIC-VC, LIC-VC%VC, TLC, FRC, PCF_{LIC} and PCF_{LIC}-PCF. *P*-values in bold indicate statistically significant values ($p<0.05$).

11.4.2 BETWEEN DISEASE COMPARISONS OF THE IMMEDIATE EFFECT OF LVR

MND *vs.* Other Δ Time 0b – 0a	n	Mean difference	95% CI		*p*-value
LIC	26 : 52	0.04	-0.13	0.21	0.670
VC	26 : 52	-0.04	-0.12	0.04	0.359
LIC – VC	26 : 52	0.07	-0.10	0.25	0.406
C_{rs}	19 : 46	0.0038	0.0030	0.0187	**0.008**
Specific C_{rs}	10 : 34	-0.0018	-0.0088	0.0052	0.607
PCF	26 : 52	16.5	-3.3	36.3	0.101
PCF_{LIC}	26 : 51	-7.4	-24.1	9.3	0.380
PCF_{LIC} – PCF	26 : 51	-24.1	-51.2	3.0	0.081
FRC	11 : 38	-0.16	-0.31	-0.02	**0.027**
TLC	11 : 38	-0.19	-0.33	-0.05	**0.007**
RV	11 : 38	-0.16	-0.29	-0.02	**0.027**
ERV	11 : 38	-0.01	-0.09	0.08	0.864
IC	11 : 38	-0.04	-0.14	0.05	0.374

Table 11-13: Post-hoc comparisons of the mean difference between MND and Other NMD sub-groups in the change pre-post a single-session of LVR (Time 0b minus Time 0a).

(n) = number of participants; Time = Timepoint; MND = motor neurone disease group, Other = Other neuromuscular disease group. Shaded cells refer to comparisons that were statistically significant in the linear mixed models. *P*-values in bold indicate statistically significant values ($p<0.05$).

11.5 RANDOMISED CONTROLLED TRIAL: EFFECT OF REGULAR LVR

11.5.1 THERAPY USAGE

	LVR (n=37)		Control (n=39)		
	mean±SD	**median(range)**	**mean±SD**	**median(range)**	***P*-value**
Study duration (days)	88.5 (12.5)	90 (33 – 110)	90.6 (4.1)	90 (82 – 104)	0.335
Average sessions/day	1.2 (0.7)	1.2 (0.0 – 2.3)	1.5 (0.5)	1.7 (0.1 – 2.0)	**0.015**
Zero/day (%)	29.9 (33.6)	17.8 (0 – 99.1)	13.7 (22.9)	4.5 (0 – 94.0)	*0.078*
Once/day (%)	21.3 (21.9)	13.1 (0 – 82.6)	19.0 (19.9)	13.0 (0 – 81.9)	*0.670*
Two plus/day (%)	48.7 (39.5)	45.3 (0 – 100)	67.3 (27.8)	75.3 (4.8 – 100)	*0.060*

Table 11-14: Summary statistics and between-group comparisons of therapy usage, taken from participant diaries

Data are presented as mean ± standard deviation, and median (minimum – maximum).
LVR = all participants randomised to lung volume recruitment group, Control = active control group. One participant withdrew at Timepoint 1 (diary data to Day 33 included) and two further participants did not complete Timepoint 3a (diary data to Timepoint 2 / last contact included). Zero/day = proportion of days no therapy sessions were conducted (%); Once/day = proportion of days one therapy session was conducted (%); Two plus/day = proportion of days at least two therapy sessions were conducted (i.e., the prescribed dose) (%).
P-values refer to two-sampled Student's t-test for normally distributed data, or Mann-Whitney U-test for non-normally distributed data (italics).
A p-value < 0.05 was considered statistically significant (bold).

11.5.2 RESPIRATORY FUNCTION BY TREATMENT GROUP AND DISEASE SUB-GROUP, AT EACH STUDY TIMEPOINT (TIME 0A, 1, 2, 3A)

Variable	Timepoint 0a		Timepoint 1		Timepoint 2		Timepoint 3a	
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**	**LVR**	**Control**
LIC (L)								
All	1.99 ± 1.05 (37)	1.97 ± 1.03 (39)	2.13 ± 1.01 (35)	1.81 ± 0.92 (38)	2.09 ± 1.04 (35)	1.87 ± 0.95 (39)	2.01 ± 1.02 (33)*	1.91 ± 0.92 (39)
MND	2.54 ± 0.94 (12)	2.77 ± 1.22 (13)	2.78 ± 0.88 (10)	2.53 ± 1.12 (12)	2.72 ± 0.89 (10)	2.45 ± 1.18 (13)	2.57 ± 1.07 (10)	2.53 ± 0.99 (13)
Other	1.73 ± 1.02 (25)	1.58 ± 0.64 (26)	1.87 ± 0.95 (25)	1.48 ± 0.59 (26)	1.83 ± 1.01 (25)	1.58 ± 0.67 (26)	1.77 ± 0.92 (23)*	1.59 ± 0.71 (26)
VC (L)								
All	1.58 ± 0.88 (37)	1.50 ± 0.83 (39)	1.59 ± 0.88 (35)	1.48 ± 0.86 (38)	1.59 ± 0.90 (35)	1.44 ± 0.81 (39)	1.48 ± 0.86 (34)	1.42 ± 0.79 (39)*
MND	2.00 ± 0.62 (12)	2.20 ± 0.85 (13)	2.04 ± 0.58 (10)	2.12 ± 1.02 (12)	2.11 ± 0.63 (10)	1.99 ± 0.92 (13)	1.78 ± 0.71 (10)*	1.93 ± 0.89 (13)*
Other	1.38 ± 0.93 (25)	1.16 ± 0.57 (26)	1.41 ± 0.93 (25)	1.18 ± 0.59 (26)	1.38 ± 0.91 (25)	1.16 ± 0.59 (26)	1.35 ± 0.89 (24)	1.16 ± 0.60 (26)
LIC-VC (L)								
All	0.41 ± 0.54 (37)	0.47 ± 0.43 (39)	0.54 ± 0.51 (35)	0.34 ± 0.39 (38)	0.50 ± 0.43 (35)	0.43 ± 0.42 (39)	0.56 ± 0.52 (33)*	0.49 ± 0.43 (39)
MND	0.55 ± 0.73 (12)	0.57 ± 0.56 (13)	0.74 ± 0.56 (10)	0.41 ± 0.54 (12)	0.61 ± 0.55 (10)	0.45 ± 0.58 (13)	0.79 ± 0.55 (10)	0.60 ± 0.59 (13)
Other	0.41 ± 0.42 (25)	0.42 ± 0.35 (26)	0.46 ± 0.47 (25)	0.30 ± 0.31 (26)	0.45 ± 0.38 (25)	0.41 ± 0.33 (26)	0.46 ± 0.48 (23)*	0.43 ± 0.32 (26)
LIC-VC (%VC)								
All	34 ± 47 (37)	41 ± 45 (39)	45 ± 43 (35)	35 ± 42 (38)	40 ± 35 (35)	43 ± 50 (39)	49 ± 42 (33)*	49 ± 56 (39)
MND	32 ± 42 (12)	26 ± 19 (13)	38 ± 26 (10)	32 ± 50 (12)	30 ± 29 (10)	35 ± 60 (13)	50 ± 45 (10)	52 ± 74 (13)
Other	35 ± 50 (25)	49 ± 52 (26)	48 ± 48 (25)	37 ± 39 (26)	44 ± 36 (25)	48 ± 45 (26)	49 ± 42 (23)	48 ± 47 (26)
C_{rs} (L/cmH_2O)								
All	0.035 ± 0.020 (35)	0.040 ± 0.030 (34)	0.041 ± 0.020 (35)	0.043 ± 0.027 (37)	0.041 ± 0.020 (35)	0.042 ± 0.025 (38)	0.041 ± 0.028 (30)*	0.043 ± 0.029 (36)
MND	0.041 ± 0.015 (11)	0.055 ± 0.033 (10)	0.052 ± 0.016 (10)	0.054 ± 0.029 (12)	0.054 ± 0.018 (10)	0.053 ± 0.031 (13)	0.063 ± 0.030 (8)	0.058 ± 0.035 (12)
Other	0.032 ± 0.022 (24)	0.033 ± 0.028 (24)	0.036 ± 0.020 (25)	0.037 ± 0.025 (25)	0.035 ± 0.018 (25)	0.036 ± 0.020 (25)	0.033 ± 0.024 (22)	0.036 ± 0.022 (24)
Specific C_{rs} ($L/cmH_2O/L$)								
All	0.031 ± 0.017 (28)	0.034 ± 0.038 (29)	0.036 ± 0.022 (31)	0.039 ± 0.046 (32)	0.035 ± 0.019 (26)	0.034 ± 0.028 (31)	0.048 ± 0.042 (24)*	0.040 ± 0.034 (31)
MND	0.027 ± 0.014 (7)	0.026 ± 0.011 (8)	0.027 ± 0.013 (9)	0.027 ± 0.014 (9)	0.034 ± 0.019 (7)	0.023 ± 0.014 (10)	0.038 ± 0.027 (5)	0.027 ± 0.011 (8)
Other	0.033 ± 0.018 (21)	0.038 ± 0.044 (21)	0.040 ± 0.023 (22)	0.044 ± 0.054 (23)	0.036 ± 0.020 (19)	0.039 ± 0.031 (21)	0.051 ± 0.045 (19)*	0.045 ± 0.038 (23)

Variable	Timepoint 0a		Timepoint 1		Timepoint 2		Timepoint 3a	
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**	**LVR**	**Control**
PCF (L/min)								
All	173 ± 59 (37)	177 ± 80 (39)	168 ± 58 (35)	168 ± 62 (38)	167 ± 58 (35)	165 ± 63 (39)	154 ± 50 (34)*	169 ± 64 (39)
MND	180 ± 66 (12)	192 ± 62 (13)	194 ± 70 (10)	183 ± 78 (12)	188 ± 76 (10)	171 ± 75 (13)	154 ± 66 (10)*	176 ± 70 (13)
Other	169 ± 57 (25)	170 ± 87 (26)	158 ± 51 (25)	161 ± 53 (26)	158 ± 49 (25)	162 ± 58 (26)	154 ± 43 (24)	166 ± 61 (26)
PCF_{UC} (L/min)								
All	165 ± 49 (37)	183 ± 62 (39)	187 ± 62 (35)	185 ± 62 (38)	182 ± 55 (35)	188 ± 52 (39)	183 ± 59 (33)*	185 ± 57 (39)
MND	168 ± 53 (12)	215 ± 68 (13)	191 ± 57 (10)	210 ± 69 (12)	187 ± 51 (10)	204 ± 67 (13)	178 ± 41 (10)	200 ± 61 (13)
Other	164 ± 47 (25)	166 ± 53 (26)	185 ± 65 (25)	173 ± 57 (26)	181 ± 58 (25)	180 ± 43 (26)	185 ± 62 (23)*	177 ± 55 (26)
PCF_{UC} – PCF (L/min)								
All	-7 ± 39 (37)	5 ± 61 (39)	19 ± 45 (35)	17 ± 41 (38)	16 ± 44 (35)	23 ± 39 (39)	31 ± 35 (33)*	16 ± 39 (39)
MND	-12 ± 31 (12)	24 ± 45 (13)	-3 ± 55 (10)	28 ± 34 (12)	-1 ± 53 (10)	33 ± 46 (13)	24 ± 36 (10)*	25 ± 41 (13)
Other	-5 ± 43 (25)	-4 ± 67 (26)	27 ± 39 (25)	13 ± 44 (26)	23 ± 38 (25)	18 ± 35 (26)	33 ± 36 (23)*	11 ± 37 (26)
MIP (cmH_2O)								
All	35.1 ± 18.3 (36)	43.1 ± 22.1 (37)	N/A	N/A	N/A	N/A	34.5 ± 17.9 (30)	41.0 ± 20.8 (37)
MND	32.9 ± 18.9 (11)	41.5 ± 18.5 (12)					34.9 ± 17.6 (7)	34.3 ± 16.3 (12)*
Other	36.0 ± 18.3 (25)	43.8 ± 23.9 (25)					34.4 ± 18.4 (23)	44.3 ± 22.1 (25)
MEP (cmH_2O)								
All	48.0 ± 26.2 (34)	49.0 ± 27.4 (32)	N/A	N/A	N/A	N/A	42.3 ± 23.4 (31)	50.4 ± 30.8 (33)
MND	44.8 ± 24.4 (12)	55.0 ± 29.7 (8)					43.1 ± 22.5 (8)*	50.4 ± 32.4 (9)*
Other	49.8 ± 27.6 (22)	47.0 ± 26.9 (24)					42.0 ± 24.2 (23)	50.4 ± 30.9 (24)
SNIP (cmH_2O)								
All	23.1 ± 12.7 (37)	28.7 ± 14.4 (37)	N/A	N/A	N/A	N/A	24.5 ± 12.9 (31)	27.9 ± 16.2 (37)
MND	20.1 ± 8.4 (12)	25.6 ± 9.1 (12)					19.0 ± 7.4 (8)	19.6 ± 8.3 (12)*
Other	24.5 ± 14.2 (25)	30.1 ± 16.5 (25)					26.4 ± 13.9 (23)	31.8 ± 17.6 (25)

Variable	Timepoint 0a		Timepoint 1		Timepoint 2		Timepoint 3a	
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**	**LVR**	**Control**
IC (L)								
All	1.25 ± 0.70 (30)	1.19 ± 0.56 (32)	1.30 ± 0.73 (31)	1.14 ± 0.64 (33)	1.26 ± 0.62 (26)	1.15 ± 0.57 (32)	1.18 ± 0.67 (27)	1.14 ± 0.54 (33)
MND	1.47 ± 0.47 (8)	1.58 ± 0.62 (10)	1.54 ± 0.46 (9)	1.59 ± 0.84 (9)	1.55 ± 0.32 (7)	1.57 ± 0.57 (10)	1.37 ± 0.42 (6)*	1.48 ± 0.57 (9)*
Other	1.17 ± 0.76 (22)	1.01 ± 0.43 (22)	1.20 ± 0.81 (22)	0.97 ± 0.47 (24)	1.15 ± 0.67 (19)	0.96 ± 0.47 (22)	1.12 ± 0.73 (21)	1.01 ± 0.49 (24)
ERV (L)								
All	0.39 ± 0.28 (30)	0.38 ± 0.37 (32)	0.44 ± 0.32 (31)	0.38 ± 0.36 (33)	0.42 ± 0.34 (26)	0.41 ± 0.34 (32)	0.37 ± 0.32 (27)	0.36 ± 0.34 (33)
MND	0.51 ± 0.41 (8)	0.71 ± 0.49 (10)	0.54 ± 0.36 (9)	0.73 ± 0.50 (9)	0.51 ± 0.45 (7)	0.74 ± 0.38 (10)	0.61 ± 0.37 (6)	0.75 ± 0.40 (9)
Other	0.35 ± 0.22 (22)	0.23 ± 0.17 (22)	0.40 ± 0.30 (22)	0.25 ± 0.17 (24)	0.39 ± 0.30 (19)	0.26 ± 0.17 (22)	0.31 ± 0.28 (21)	0.22 ± 0.17 (24)
FRC (L)								
All	1.31 ± 0.76 (30)	1.45 ± 1.07 (32)	1.47 ± 0.98 (31)	1.43 ± 1.15 (33)	1.43 ± 0.89 (26)	1.65 ± 1.19 (32)	1.31 ± 0.92 (27)	1.52 ± 1.15 (33)
MND	1.80 ± 0.98 (8)	2.35 ± 1.23 (10)	2.27 ± 1.16 (9)	2.45 ± 1.40 (9)	2.08 ± 1.11 (7)	2.58 ± 1.21 (10)	2.16 ± 1.14 (6)	2.66 ± 1.31 (9)
Other	1.13 ± 0.59 (22)	1.05 ± 0.70 (22)	1.15 ± 0.69 (22)	1.18 ± 0.84 (24)	1.19 ± 0.68 (19)	1.23 ± 0.93 (22)	1.07 ± 0.71 (21)	1.09 ± 0.74 (24)
RV (L)								
All	0.92 ± 0.53 (30)	1.08 ± 0.79 (32)	1.03 ± 0.76 (31)	1.15 ± 0.93 (33)	1.01 ± 0.61 (26)	1.24 ± 1.01 (32)	0.94 ± 0.64 (27)	1.16 ± 0.92 (33)
MND	1.30 ± 0.65 (8)	1.64 ± 0.79 (10)	1.73 ± 0.94 (9)	1.72 ± 1.02 (9)	1.58 ± 0.70 (7)	1.83 ± 0.98 (10)	1.55 ± 0.79 (6)	1.91 ± 1.01 (9)
Other	0.79 ± 0.43 (22)	0.82 ± 0.66 (22)	0.75 ± 0.45 (22)	0.94 ± 0.81 (24)	0.81 ± 0.44 (19)	0.97 ± 0.92 (22)	0.76 ± 0.48 (21)	0.88 ± 0.72 (24)
TLC (L)								
All	2.57 ± 1.23 (30)	2.65 ± 1.47 (32)	2.73 ± 1.46 (31)	2.67 ± 1.50 (33)	2.69 ± 1.31 (26)	2.79 ± 1.50 (32)	2.48 ± 1.34 (27)	2.67 ± 1.45 (33)
MND	3.27 ± 1.20 (8)	3.93 ± 1.71 (10)	3.80 ± 1.52 (9)	4.04 ± 1.74 (9)	3.63 ± 1.20 (7)	4.12 ± 1.44 (10)	3.53 ± 1.33 (6)	4.16 ± 1.55 (9)
Other	2.32 ± 1.17 (22)	2.06 ± 0.90 (22)	2.29 ± 1.22 (22)	2.15 ± 1.04 (24)	2.35 ± 1.20 (19)	2.18 ± 1.10 (22)	2.19 ± 1.22 (21)	2.11 ± 0.95 (24)

Table 11-15: Summary statistics of respiratory function at each timepoint, grouped by intervention

* indicates statistically significant change over time (Timepoint 3a minus Timepoint 0a) within-group, using paired Student's t-test (p-value<0.05).

11.5.3 POST-HOC COMPARISONS: OUTCOME MEASURES BY TREATMENT GROUP AND DISEASE SUB-GROUP, TIME 0A VS TIME 3A

Variable	Timepoint 0a		Timepoint 3a		Mean change over time (95% CI), *p*-value		Between-group mean difference (95% CI)	*p*-value
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**		
LIC (L)								
All	1.99 ± 1.05 (37)	1.97 ± 1.03 (39)	2.01 ± 1.02 (33)	1.91 ± 0.92 (39)	0.13 (0.01, 0.25) **0.039**	-0.07 (-0.22, 0.09) 0.380	0.19 (0.00, 0.39)	0.054
MND	2.54 ± 0.94 (12)	2.77 ± 1.22 (13)	2.57 ± 1.07 (10)	2.53 ± 0.99 (13)	0.02 (-0.34, 0.38) 0.889	-0.24 (-0.64, 0.16) 0.221		
Other	1.73 ± 1.02 (25)	1.58 ± 0.64 (26)	1.77 ± 0.92 (23)	1.59 ± 0.71 (26)	0.17 (0.07, 0.27) **0.002**	0.02 (-0.12, 0.15) 0.795		
VC (L)								
All	1.58 ± 0.88 (37)	1.50 ± 0.83 (39)	1.48 ± 0.86 (34)	1.42 ± 0.79 (39)	-0.06 (-0.13, 0.01) 0.078	-0.08 (-0.16, 0.00) **0.038**	0.02 (-0.08, 0.13)	0.645
MND	2.00 ± 0.62 (12)	2.20 ± 0.85 (13)	1.78 ± 0.71 (10)	1.93 ± 0.89 (13)	-0.23 (-0.36, -0.09) **0.004**	-0.27 (-0.45, -0.08) **0.010**		
Other	1.38 ± 0.93 (25)	1.16 ± 0.57 (26)	1.35 ± 0.89 (24)	1.16 ± 0.60 (26)	0.01 (-0.05, 0.07) 0.738	0.01 (-0.05, 0.06) 0.784		
LIC-VC (L)								
All	0.41 ± 0.54 (37)	0.47 ± 0.43 (39)	0.56 ± 0.52 (33)	0.49 ± 0.43 (39)	0.19 (0.09, 0.30) **0.0008**	0.02 (-0.12, 0.15) 0.812	0.18 (0.00, 0.35)	**0.047**
MND	0.55 ± 0.73 (12)	0.57 ± 0.56 (13)	0.79 ± 0.55 (10)	0.60 ± 0.59 (13)	0.25 (-0.04, 0.54) 0.082	0.03 (-0.33, 0.39) 0.865		
Other	0.41 ± 0.42 (25)	0.42 ± 0.35 (26)	0.46 ± 0.48 (23)	0.43 ± 0.32 (26)	0.17 (0.06, 0.28) **0.004**	0.01 (-0.12, 0.14) 0.874		
LIC-VC (%VC)								
All	34 ± 47 (37)	41 ± 45 (39)	49 ± 42 (33)*	49 ± 56 (39)				
MND	32 ± 42 (12)	26 ± 19 (13)	50 ± 45 (10)	52 ± 74 (13)				
Other	35 ± 50 (25)	49 ± 52 (26)	49 ± 42 (23)	48 ± 47 (26)				

Variable	Timepoint 0a		Timepoint 3a		Mean change over time (95% CI), *p*-value		Between-group mean difference (95% CI)	*p*-value
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**		
C_{rs} (L/cmH_2O)								
All	0.035 ± 0.020 (35)	0.040 ± 0.030 (34)	0.041 ± 0.028 (30)	0.043 ± 0.029 (36)	0.0063 (0.0004, 0.0121) **0.036**	0.0048 (-0.0038, 0.0133) 0.267	0.0015 (-0.0088, 0.0118)	0.773
MND	0.041 ± 0.015 (11)	0.055 ± 0.033 (10)	0.063 ± 0.030 (8)	0.058 ± 0.035 (12)	0.0144 (-0.0077, 0.0365) 0.168	0.0044 (-0.0180, 0.0268) 0.669		
Other	0.032 ± 0.022 (24)	0.033 ± 0.028 (24)	0.033 ± 0.024 (22)	0.036 ± 0.022 (24)	0.0033 (-0.0030, 0.0069) 0.070	0.0049 (-0.0055, 0.0232) 0.270		
Specific C_{rs} (L/cmH_2O/L)								
All	0.031 ± 0.017 (28)	0.034 ± 0.038 (29)	0.048 ± 0.042 (24)	0.040 ± 0.034 (31)	0.0160 (0.0032, 0.0287) **0.016**	0.0067 (-0.0013, 0.0148) 0.097	0.0093 (-0.0053, 0.0238)	0.207
MND	0.027 ± 0.014 (7)	0.026 ± 0.011 (8)	0.038 ± 0.027 (5)	0.027 ± 0.011 (8)	0.0062 (-0.0086, 0.0210) 0.332	0.0022 (-0.0077, 0.0121) 0.595		
Other	0.033 ± 0.018 (21)	0.038 ± 0.044 (21)	0.051 ± 0.045 (19)	0.045 ± 0.038 (23)	0.0191 (0.0026, 0.0356) **0.026**	0.0081 (-0.0023, 0.0184) 0.118		
FRC (L)								
All	1.31 ± 0.76 (30)	1.45 ± 1.07 (32)	1.31 ± 0.92 (27)	1.52 ± 1.15 (33)	-0.02 (-0.15, 0.10) 0.695	0.06 (-0.09, 0.21) 0.413	-0.09 (-0.28, 0.11)	0.383
MND	1.80 ± 0.98 (8)	2.35 ± 1.23 (10)	2.16 ± 1.14 (6)	2.66 ± 1.31 (9)	0.05 (-0.34, 0.44) 0.742	0.10 (-0.44, 0.64) 0.667		
Other	1.13 ± 0.59 (22)	1.05 ± 0.70 (22)	1.07 ± 0.71 (21)	1.09 ± 0.74 (24)	-0.05 (-0.19, 0.10) 0.501	0.05 (-0.08, 0.18) 0.468		
RV (L)								
All	0.92 ± 0.53 (30)	1.08 ± 0.79 (32)	0.94 ± 0.64 (27)	1.16 ± 0.92 (33)	0.00 (-0.11, 0.10) 0.938	0.11 (-0.04, 0.25) 0.162	-0.11 (-0.29, 0.07)	0.237
MND	1.30 ± 0.65 (8)	1.64 ± 0.79 (10)	1.55 ± 0.79 (6)	1.91 ± 1.01 (9)	0.07 (-0.36, 0.49) 0.709	0.19 (-0.37, 0.75) 0.451		
Other	0.79 ± 0.43 (22)	0.82 ± 0.66 (22)	0.76 ± 0.48 (21)	0.88 ± 0.72 (24)	-0.02 (-0.12, 0.08) 0.624	0.07 (-0.04, 0.19) 0.192		

Variable	Timepoint 0a		Timepoint 3a		Mean change over time (95% CI), *p*-value		Between-group mean difference (95% CI)	*p*-value
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**		
TLC (L)								
All	2.57 ± 1.23 (30)	2.65 ± 1.47 (32)	2.48 ± 1.34 (27)	2.67 ± 1.45 (33)	-0.09 (-0.21, 0.03) 0.131	0.01 (-0.14, 0.15) 0.924	-0.10 (-0.28, 0.09)	0.292
MND	3.27 ± 1.20 (8)	3.93 ± 1.71 (10)	3.53 ± 1.33 (6)	4.16 ± 1.55 (9)	-0.10 (-0.57, 0.37) 0.598	-0.13 (-0.64, 0.39) 0.581		
Other	2.32 ± 1.17 (22)	2.06 ± 0.90 (22)	2.19 ± 1.22 (21)	2.11 ± 0.95 (24)	-0.09 (-0.21, 0.03) 0.142	0.05 (-0.06, 0.17) 0.323		
ERV (L)								
All	0.39 ± 0.28 (30)	0.38 ± 0.37 (32)	0.37 ± 0.32 (27)	0.36 ± 0.34 (33)	-0.02 (-0.08, 0.04) 0.500	-0.04 (-0.09, 0.00) 0.072	0.02 (-0.05, 0.10)	0.538
MND	0.51 ± 0.41 (8)	0.71 ± 0.49 (10)	0.61 ± 0.37 (6)	0.75 ± 0.40 (9)	-0.01 (-0.15, 0.13) 0.820	-0.09 (-0.23, 0.05) 0.177		
Other	0.35 ± 0.22 (22)	0.23 ± 0.17 (22)	0.31 ± 0.28 (21)	0.22 ± 0.17 (24)	-0.02 (-0.10, 0.05) 0.536	-0.03 (-0.08, 0.02) 0.262		
IC (L)								
All	1.25 ± 0.70 (30)	1.19 ± 0.56 (32)	1.18 ± 0.67 (27)	1.14 ± 0.54 (33)	-0.05 (-0.11, 0.00) 0.072	-0.06 (-0.14, 0.01) 0.097	0.01 (-0.08, 0.11)	0.793
MND	1.47 ± 0.47 (8)	1.58 ± 0.62 (10)	1.37 ± 0.42 (6)	1.48 ± 0.57 (9)	-0.16 (-0.30, -0.01) **0.042**	-0.27 (-0.48, -0.05) **0.021**		
Other	1.17 ± 0.76 (22)	1.01 ± 0.43 (22)	1.12 ± 0.73 (21)	1.01 ± 0.49 (24)	-0.02 (-0.08, 0.04) 0.452	0.01 (-0.04, 0.06) 0.697		
PCF (L/min)								
All	173 ± 59 (37)	177 ± 80 (39)	154 ± 50 (34)	169 ± 64 (39)	-15.4 (-25.7, -5.2) **0.004**	-8.0 (-23.4, 7.5) 0.303	-7.5 (-26.3, 11.3)	0.430
MND	180 ± 66 (12)	192 ± 62 (13)	154 ± 66 (10)	176 ± 70 (13)	-28.0 (-47.1, -8.9) **0.009**	-15.9 (-38.1, 6.2) 0.143		
Other	169 ± 57 (25)	170 ± 87 (26)	154 ± 43 (24)	166 ± 61 (26)	-10.2 (-22.6, 2.2) 0.103	-4.0 (-25.1, 17.2) 0.702		

Variable	Timepoint 0a		Timepoint 3a		Mean change over time (95% CI), *p*-value		Between-group mean difference (95% CI)	*p*-value
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**		
PCF_{UC} (L/min)								
All	165 ± 49 (37)	183 ± 62 (39)	183 ± 59 (33)	185 ± 57 (39)	19.6 (6.4, 32.8) **0.005**	2.3 (-10.7, 15.3) 0.723	17.3 (-0.9, 35.6)	0.063
MND	168 ± 53 (12)	215 ± 68 (13)	178 ± 41 (10)	200 ± 61 (13)	3.8 (-8.6, 16.2) 0.505	-14.7 (-39.1, 9.7) 0.213		
Other	164 ± 47 (25)	166 ± 53 (26)	185 ± 62 (23)	177 ± 55 (26)	26.5 (8.5, 44.4) **0.006**	10.8 (-4.5, 26.0) 0.158		
PCF_{UC} – PCF (L/min)								
All	-7 ± 39 (37)	5 ± 61 (39)	31 ± 35 (33)	16 ± 39 (39)	35.7 (18.4, 53.1) **0.0002**	10.2 (-6.4, 26.9) 0.221	25.5 (1.7, 49.2)	**0.036**
MND	-12 ± 31 (12)	24 ± 45 (13)	24 ± 36 (10)	25 ± 41 (13)	31.8 (12.8, 50.9) **0.004**	1.2 (-28.0, 30.4) 0.928		
Other	-5 ± 43 (25)	-4 ± 67 (26)	33 ± 36 (23)	11 ± 37 (26)	37.4 (13.0, 61.9) **0.004**	14.7 (-6.8, 36.2) 0.170		
MIP (cmH_2O)								
All	35.1 ± 18.3 (36)	43.1 ± 22.1 (37)	34.5 ± 17.9 (30)	41.0 ± 20.8 (37)	-1.8 (-4.2, 0.6) 0.144	-2.0 (-4.9, 0.8) 0.154	0.3 (-3.5, 4.0)	0.889
MND	32.9 ± 18.9 (11)	41.5 ± 18.5 (12)	34.9 ± 17.6 (7)	34.3 ± 16.3 (12)	-5.1 (-11.9, 1.7) 0.115	-7.2 (-12.3, -2.1) **0.010**		
Other	36.0 ± 18.3 (25)	43.8 ± 23.9 (25)	34.4 ± 18.4 (23)	44.3 ± 22.1 (25)	-0.8 (-3.4, 1.8) 0.550	0.4 (-2.8, 3.6) 0.781		
SNIP (cmH_2O)								
All	23.1 ± 12.7 (37)	28.7 ± 14.4 (37)	24.5 ± 12.9 (31)	27.9 ± 16.2 (37)	0.5 (-3.0, 3.9) 0.788	-0.8 (-3.6, 2.1) 0.574	1.3 (-3.1, 5.6)	0.566
MND	20.1 ± 8.4 (12)	25.6 ± 9.1 (12)	19.0 ± 7.4 (8)	19.6 ± 8.3 (12)	-2.9 (-8.3, 2.4) 0.235	-6.0 (-8.9, -3.1) **0.0008**		
Other	24.5 ± 14.2 (25)	30.1 ± 16.5 (25)	26.4 ± 13.9 (23)	31.8 ± 17.6 (25)	1.6 (-2.7, 6.0) 0.443	1.7 (-2.0, 5.4) 0.349		

Variable	Timepoint 0a		Timepoint 3a		Mean change over time (95% CI), *p*-value		Between-group mean difference (95% CI)	*p*-value
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**		
MEP (cmH_2O)								
All	48.0 ± 26.2 (34)	49.0 ± 27.4 (32)	42.3 ± 23.4 (31)	50.4 ± 30.8 (33)	-2.0 (-4.6, 0.7) 0.141	-0.5 (-4.6, 3.6) 0.810	-1.5 (-6.4, 3.5)	0.556
MND	44.8 ± 24.4 (12)	55.0 ± 29.7 (8)	43.1 ± 22.5 (8)*	50.4 ± 32.4 (9)*	-4.0 (-7.2, -0.8) **0.021**	-12.0 (-16.7, -7.4) **0.0005**		
Other	49.8 ± 27.6 (22)	47.0 ± 26.9 (24)	42.0 ± 24.2 (23)	50.4 ± 30.9 (24)	-1.1 (-4.7, 2.4) 0.512	3.4 (-1.0, 7.7) 0.124		
MEP (cmH_2O)								
All	48.0 ± 26.2 (34)	49.0 ± 27.4 (32)	42.3 ± 23.4 (31)	50.4 ± 30.8 (33)	-2.0 (-4.6, 0.7) 0.141	-0.5 (-4.6, 3.6) 0.810	-1.5 (-6.4, 3.5)	0.556
MND	44.8 ± 24.4 (12)	55.0 ± 29.7 (8)	43.1 ± 22.5 (8)*	50.4 ± 32.4 (9)*	-4.0 (-7.2, -0.8) **0.021**	-12.0 (-16.7, -7.4) **0.0005**		
Other	49.8 ± 27.6 (22)	47.0 ± 26.9 (24)	42.0 ± 24.2 (23)	50.4 ± 30.9 (24)	-1.1 (-4.7, 2.4) 0.512	3.4 (-1.0, 7.7) 0.124		
AQoL-8D Total	71.2 ± 11.4 (36)	70.3 ± 10.0 (37)	71.4 ± 11.9 (31)	69.4 ± 10.2 (36)	-0.9 (-2.9, 1.0)	-0.7 (-2.4, 1.1)		0.835
Indep Living	46.8 ± 23.6	46.7 ± 20.5	47.8 ± 23.8	39.0 ± 23.8	-1.6 (-5.3, 2.1)	-6.8 (-11.5, -2.0)**		0.094
Senses	85.7 ± 8.3	84.2 ± 13.1	84.4 ± 7.8	83.4 ± 11.3	-0.2 (-2.6, 2.1)	-0.6 (-3.4, 2.2)		0.831
Pain	76.1 ± 23.0	76.8 ± 23.3	77.4 ± 24.8	76.8 ± 23.6	1.0 (-2.2, 4.2)	-0.6 (-5.7, 4.6)		0.626
Mental Health	77.4 ± 12.1	76.0 ± 10.7	79.2 ± 14.1	76.2 ± 11.5	0.4 (-2.3, 3.1)	0.1 (-2.5, 2.7)		0.868
Happiness	72.4 ± 11.8	68.1 ± 18.0	69.0 ± 15.4	68.1 ± 15.0	-4.0 (-7.4, -0.7)**	-0.5 (-3.4, 2.4)		0.110
Self Worth	67.8 ± 17.7	65.5 ± 19.1	68.5 ± 21.2	66.9 ± 18.3	-1.1 (-5.2, 3.1)	1.6 (-2.9, 6.1)		0.380
Coping	66.4 ± 12.5	62.4 ± 15.8	66.1 ± 15.5	62.8 ± 17.7	-0.8 (-5.4, 3.8)	1.2 (-2.3, 4.6)		0.480
Relationships	74.3 ± 13.0	75.2 ± 10.4	74.7 ± 12.3	75.3 ± 11.7	-1.0 (-4.1, 2.1)	0.5 (-2.2, 3.2)		0.468

Variable	Timepoint 0a		Timepoint 3a		Mean change over time (95% CI), *p*-value		Between-group mean difference (95% CI)	*p*-value
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**		
AQoL-8D Utility								
Indep Living	0.54 ± 0.17	0.52 ± 0.15	0.55 ± 0.18	0.49 ± 0.17	-0.01 (-0.03, 0.02)	-0.02 (-0.05, 0.00)		0.368
Senses	0.87 ± 0.07	0.85 ± 0.14	0.85 ± 0.11	0.86 ± 0.11	-0.01 (-0.05, 0.03)	0.01 (-0.02, 0.04)		0.430
Pain	0.78 ± 0.21	0.78 ± 0.20	0.79 ± 0.22	0.79 ± 0.21	0.01 (-0.02, 0.03)	0.00 (-0.05, 0.05)		0.821
Mental Health	0.70 ± 0.14	0.67 ± 0.12	0.72 ± 0.16	0.68 ± 0.13	0.00 (-0.03, 0.03)	0.01 (-0.03, 0.04)		0.819
Happiness	0.82 ± 0.10	0.78 ± 0.16	0.78 ± 0.14	0.78 ± 0.13	-0.04 (-0.07, -0.01)**	-0.01 (-0.03, 0.02)		0.111
Self Worth	0.76 ± 0.14	0.74 ± 0.15	0.76 ± 0.17	0.75 ± 0.15	-0.01 (-0.05, 0.02)	0.02 (-0.02, 0.06)		0.178
Coping	0.76 ± 0.11	0.72 ± 0.14	0.75 ± 0.14	0.72 ± 0.16	-0.01 (-0.05, 0.02)	0.01 (-0.02, 0.04)		0.352
Relationships	0.63 ± 0.13	0.65 ± 0.12	0.64 ± 0.12	0.65 ± 0.12	-0.01 (-0.05, 0.03)	0.01 (-0.02, 0.04)		0.469
Super Dimensions								
Physical	0.54 ± 0.16	0.52 ± 0.14	0.54 ± 0.16	0.51 ± 0.14	-0.01 (-0.03, 0.02)	-0.01 (-0.04, 0.02)		0.935
Psychosocia	0.38 ± 0.17	0.35 ± 0.16	0.38 ± 0.16	0.36 ± 0.17	-0.02 (-0.06, 0.02)	0.01 (-0.02, 0.04)		0.185
Utility Index	0.67 ± 0.17	0.64 ± 0.17	0.67 ± 0.19	0.64 ± 0.17	-0.01 (-0.04, 0.01)	0.01 (-0.02, 0.04)		0.257
SRI Summary	44.6 ± 7.7 (37)	44.3 ± 9.2 (33)	45.8 ± 8.1 (39)	46.1 ± 8.0 (39)	1.2 (-1.4, 3.7)	1.8 (-0.8, 4.4)	-0.1 (-3.6, 3.4)	0.968
Respiratory	34.0 ± 17.1	32.5 ± 20.0	37.1 ± 19.0	34.8 ± 18.4	2.9 (-2.4, 8.2)	2.2 (-2.7, 7.2)	2.1 (-4.3, 8.6)	0.511
Physical Functioning	59.2 ± 12.1	62.3 ± 13.2	61.6 ± 8.1	62.3 ± 12.0	2.4 (-1.9, 6.8)	0.0 (-4.7, 4.7)		0.176
Symptoms & Sleep	42.0 ± 8.4	41.9 ± 14.9	43.3 ± 9.4	43.6 ± 12.9	0.8 (-2.8, 4.3)	0.8 (-2.6, 4.3)		0.971

Variable	Timepoint 0a		Timepoint 3a		Mean change over time (95% CI), *p*-value		Between-group mean difference (95% CI)	*p*-value
	LVR	**Control**	**LVR**	**Control**	**LVR**	**Control**		
Social R'ships	55.1 ± 13.9	53.4 ± 15.0	56.2 ± 10.7	54.9 ± 8.3	2.0 (-1.4, 5.5)	2.1 (-2.9, 7.1)		0.984
Anxiety	30.9 ± 18.4	30.9 ± 22.0	31.0 ± 21.0	34.1 ± 23.4	0.6 (-5.7, 6.8)	3.0 (-2.1, 8.2)		0.537
Psych. Well-being	47.8 ± 9.8	51.1 ± 10.3	49.0 ± 7.9	49.3 ± 10.4	0.3 (-2.4, 2.9)	-1.7 (-4.6, 1.1)		0.294
Social Functioning	43.0 ± 14.8	37.8 ± 12.1	41.5 ± 12.7	42.9 ± 12.9	2.0 (-1.4, 5.5)	1.5 (-3.5, 6.5)	-0.1 (-6.2, 6.1)	0.984

Table 11-16: Summary statistics for respiratory function and health-related quality of life outcome measures, at baseline and final assessment, grouped by treatment (LVR vs Active Control). Data presented for the cohort, as well as by disease sub-group.

Data are presented as mean ± standard deviation, and mean difference (95% CI). *P*-value for within group mean change over time refers to Student's paired t-test; *p*-value for between group mean difference of change refers to Student's independent t-test. **Bold** values indicate comparisons that were statistically significant ($p<0.05$).

	Time 0a		Time 3a		
	mean±SD	**median(range)**	**mean±SD**	**median(range)**	***p*-value**
Bulbar					
LVR	8.2 ± 4.2	9.5 (0 – 12)	7.2 ± 3.6	7 (2 – 12)	**0.003**
Control	9.5 ± 2.8	11 (4 – 12)	8.0 ± 3.5	9 (0 – 12)	**0.011**
All MND	8.8 ± 3.5	10 (0 – 12)	7.7 ± 3.5	8 (0 – 12)	**0.0001**
Fine motor					
LVR	5.2 ± 4.2	4 (0 – 12)	4.0 ± 4.2	1.5 (0 – 11)	**0.018**
Control	5.4 ± 3.5	6 (0 – 12)	3.5 ± 3.9	2 (0 – 12)	**0.023**
All MND	5.3 ± 3.7	6 (0 – 12)	3.7 ± 4.0	2 (0 – 12)	**0.001**
Gross motor					
LVR	5.1 ± 4.2	5.5 (0 – 11)	4.8 ± 4.1	5 (0 – 11)	0.209
Control	6.5 ± 3.8	7 (0 – 12)	4.7 ± 3.3	5 (0 – 12)	**0.0009**
All MND	5.8 ± 4.0	6 (0 – 12)	4.7 ± 3.6	5 (0 – 12)	**0.0007**
Respiratory					
LVR	2.9 ± 2.9	2 (2 – 12)	2.4 ± 1.7	2 (1 – 7)	0.226
Control	5.3 ± 4.2	2 (2 – 12)	4.2 ± 4.1	2 (1 – 12)	0.131
All MND	4.2 ± 3.7	2 (2– 12)	3.4 ± 3.3	2 (1 – 12)	**0.047**
Summary					
LVR	21.3 ± 6.6	21.5 (12 – 32)	18.4 ± 6.7	17 (10 – 30)	**0.002**
Control	26.7 ± 7.1	26 (11 – 37)	20.4 ± 6.5	20 (9 – 35)	**0.002**
All MND	24.1 ± 7.2	25 (11 – 37)	19.5 ± 6.5	19 (9 – 35)	**<0.0001**

Table 11-17: Summary statistics for the Revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) at baseline and final assessment, for participants with motor neurone disease randomised to lung volume recruitment or active control treatment groups

Data are presented as mean ± standard deviation, and median (minimum – maximum).
LVR = lung volume recruitment group (n= 12 at Time 0a, n=10 at Time 3a), Control = active control group (n=13 at Times 0a and 3a), All MND = all randomised participants with motor neurone disease (n=25 Time 0a, n=23 Time 3a). P-value refers to Student's paired t-test, bold values indicate comparisons that were statistically significant within-group over time (p<0.05).

11.5.4 LINEAR MIXED MODELS

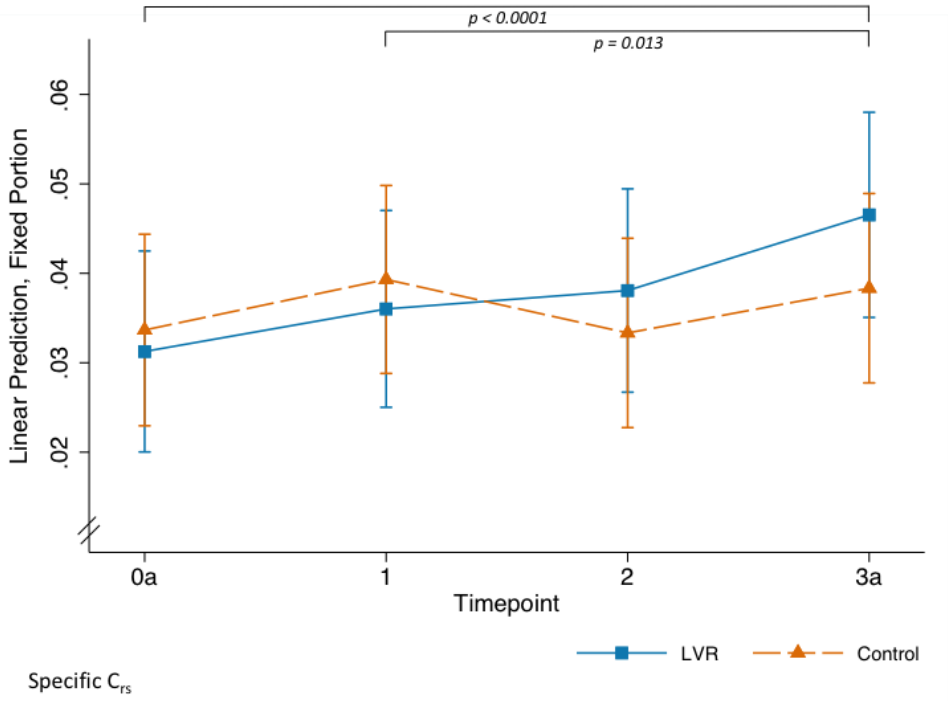

Figure 11-8: Linear mixed model of specific respiratory system compliance (Specific C_{rs}), for the whole cohort. Model significant and main effect of time present.

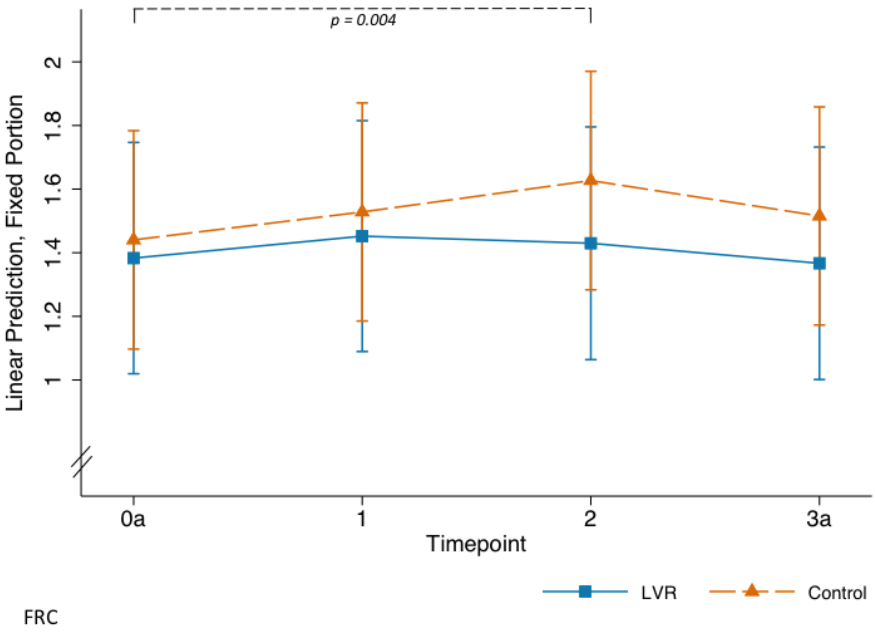

Figure 11-9: Linear mixed model of functional residual capacity (FRC), for the whole cohort. Model not significant and no main effects or interaction.

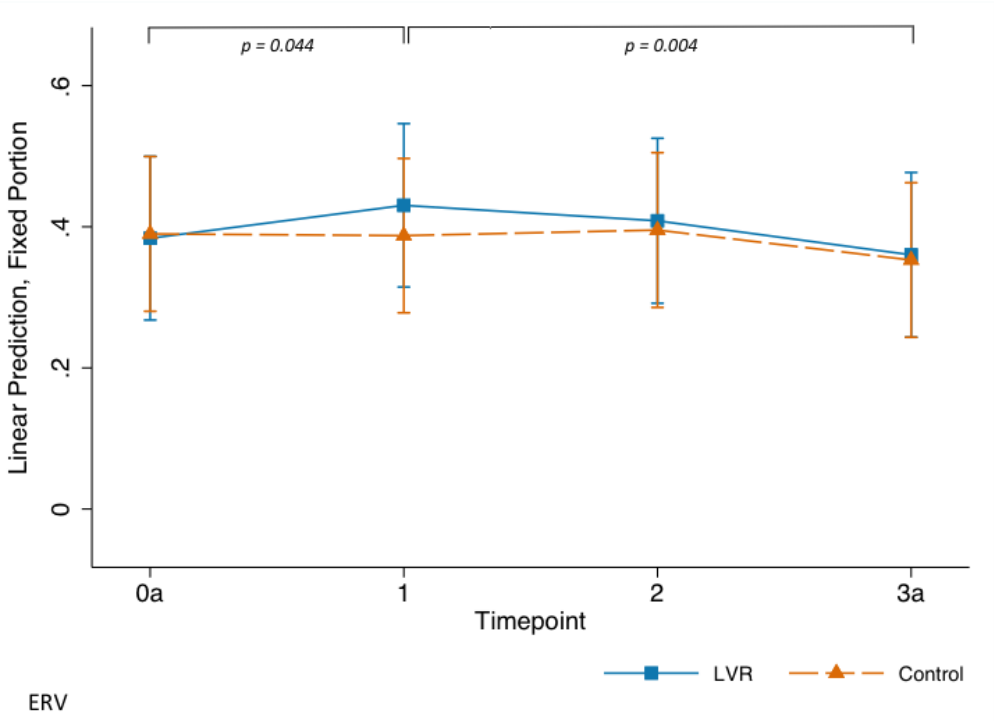

Figure 11-10: Linear mixed model of expiratory reserve volume (ERV), for the whole cohort. Model not significant however main effect of time present

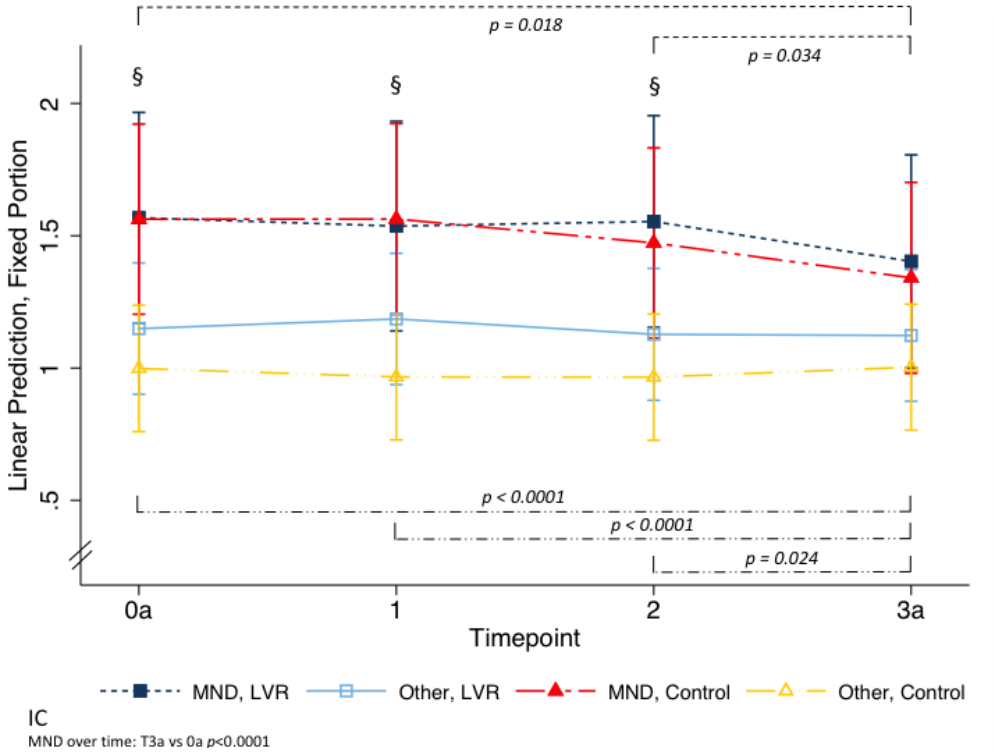

Figure 11-11: Linear mixed model of inspiratory capacity (IC), by disease type. Model significant, main effects of time, disease and time by disease interaction present.

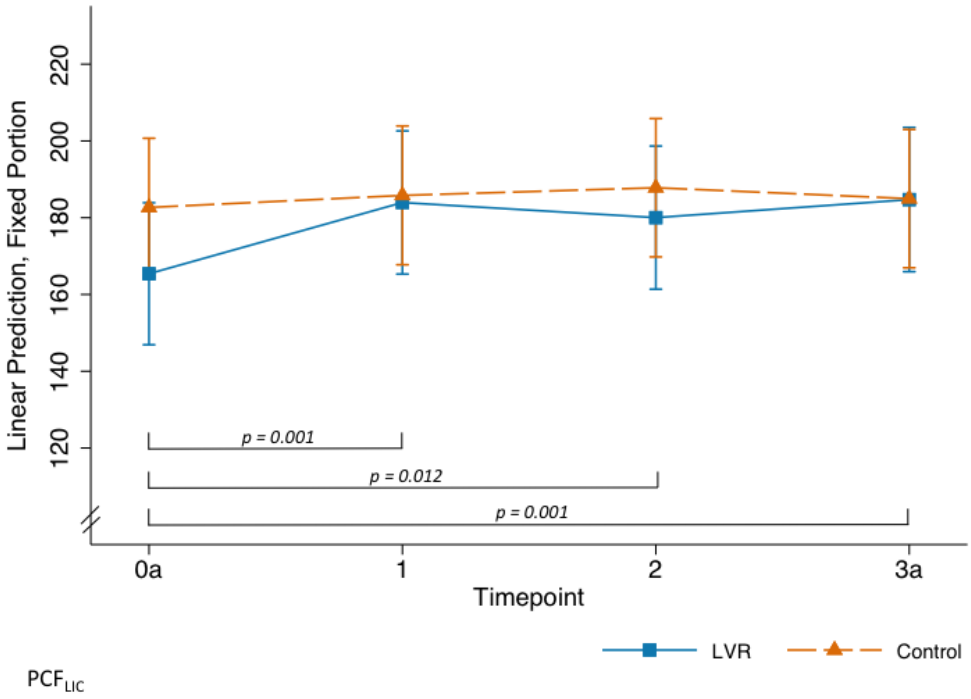

Figure 11-12: Linear mixed model of peak cough flow from lung insufflation capacity (PCF_{LIC}), for the whole cohort. Model significant and main effect of time present.

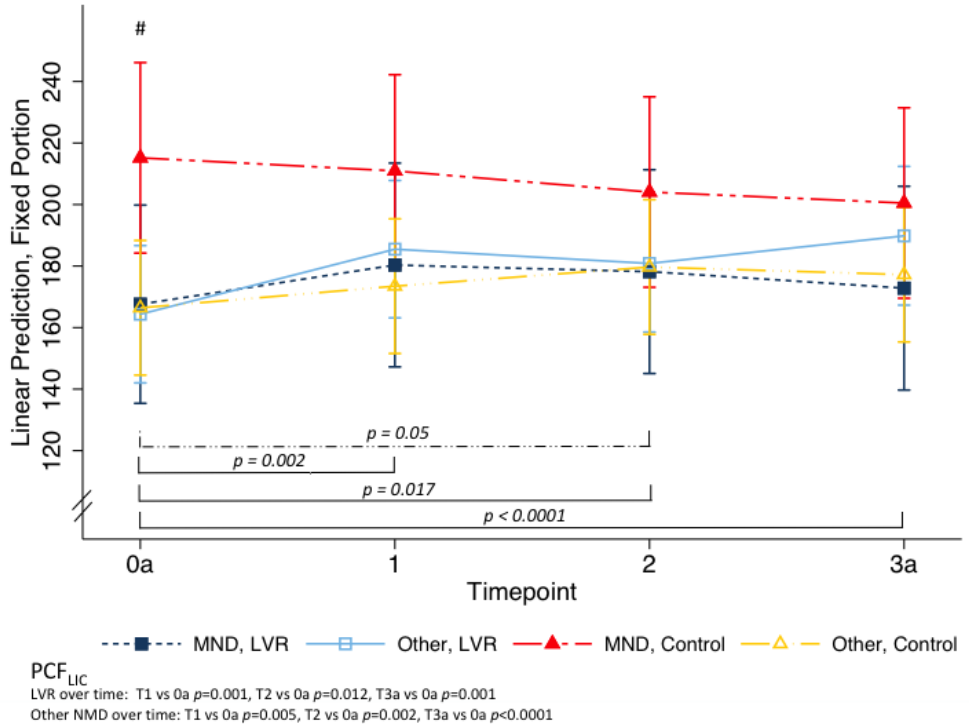

Figure 11-13: Linear mixed model of peak cough flow from lung insufflation capacity (PCF_{LIC}), by disease type. Model significant overall, however no significant main effects or interaction.

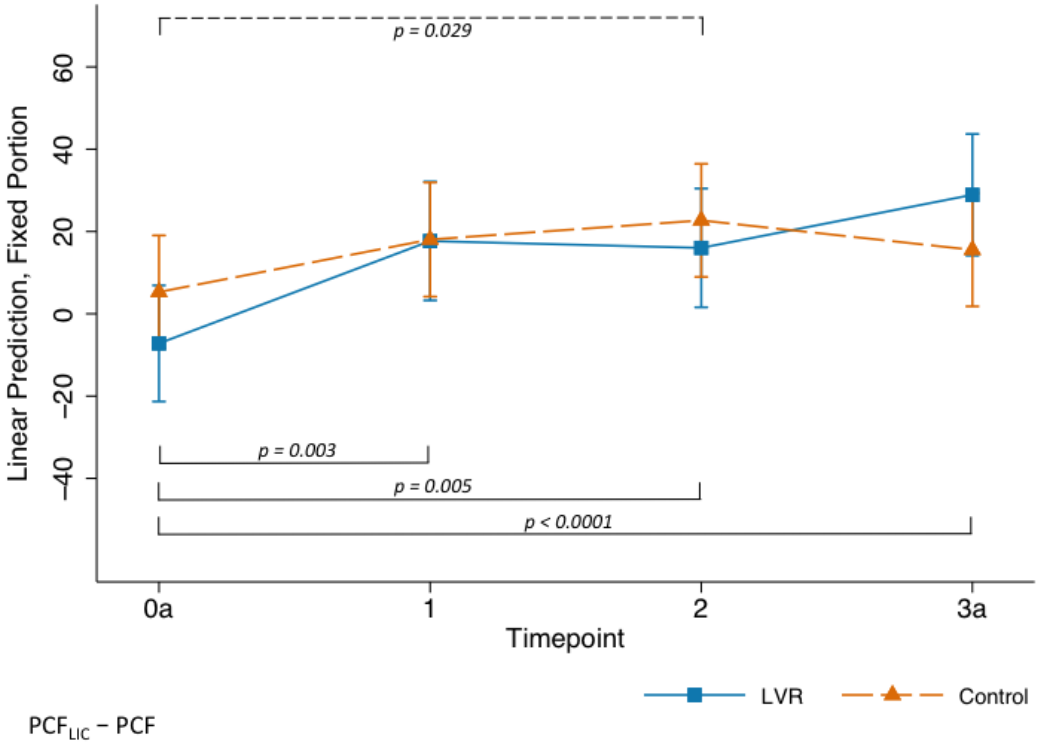

Figure 11-14: Linear mixed model of peak cough flow from lung insufflation capacity minus peak cough flow (PCF_{LIC}– PCF) difference, for the whole cohort. Model significant and main effect of time present.

	χ^2	*p*-value
AQoL-8D* Independent Living utility** ***Model 1: log restricted likelihood = 98.0	*4.2*	*0.241*
Treatment	0.54	0.463
Time	2.33	0.127
Treatment*Time	1.07	0.302
AQoL-8D* Senses utility** ***Model 1: log restricted likelihood = 113.3	*0.8*	*0.842*
Treatment	0.13	0.723
Time	0.06	0.809
Treatment*Time	0.64	0.422
AQoL-8D* Pain utility** ***Model 1: log restricted likelihood = 50.9	*0.2*	*0.984*
Treatment	0.01	0.933
Time	0.11	0.738
Treatment*Time	0.05	0.825
AQoL-8D* Mental Health utility** ***Model 1: log restricted likelihood = 104.3	*1.4*	*0.703*
Treatment	1.14	0.285
Time	0.27	0.601
Treatment*Time	0.01	0.934
AQoL-8D* Self Worth utility** ***Model 1: log restricted likelihood = 85.4	*1.8*	*0.613*
Treatment	0.09	0.764
Time	0.17	0.676
Treatment*Time	1.45	0.228
AQoL-8D* Coping utility** ***Model 1: log restricted likelihood = 95.5	*2.2*	*0.531*
Treatment	1.39	0.238
Time	0.09	0.761
Treatment*Time	0.68	0.409
AQoL-8D* Relationships utility** ***Model 1: log restricted likelihood = 106.5	*0.7*	*0.885*
Treatment	0.39	0.535
Time	0.03	0.872
Treatment*Time	0.24	0.628

Table 11-18: Linear mixed models of effect of i) Treatment and Time on Health-related quality of life in participants with neuromuscular disease.

Treatment represents Lung Volume Recruitment or Control; Time represents baseline (Time 0a) and final assessment (Time 3a); Disease indicates motor neurone disease or other neuromuscular disease; where Treatment, Time and Disease are fixed effects and participant a random effect. *P*-values in bold indicate statistically significant values ($p<0.05$). AQoL-8D = Assessment of quality of life with 8 domains.

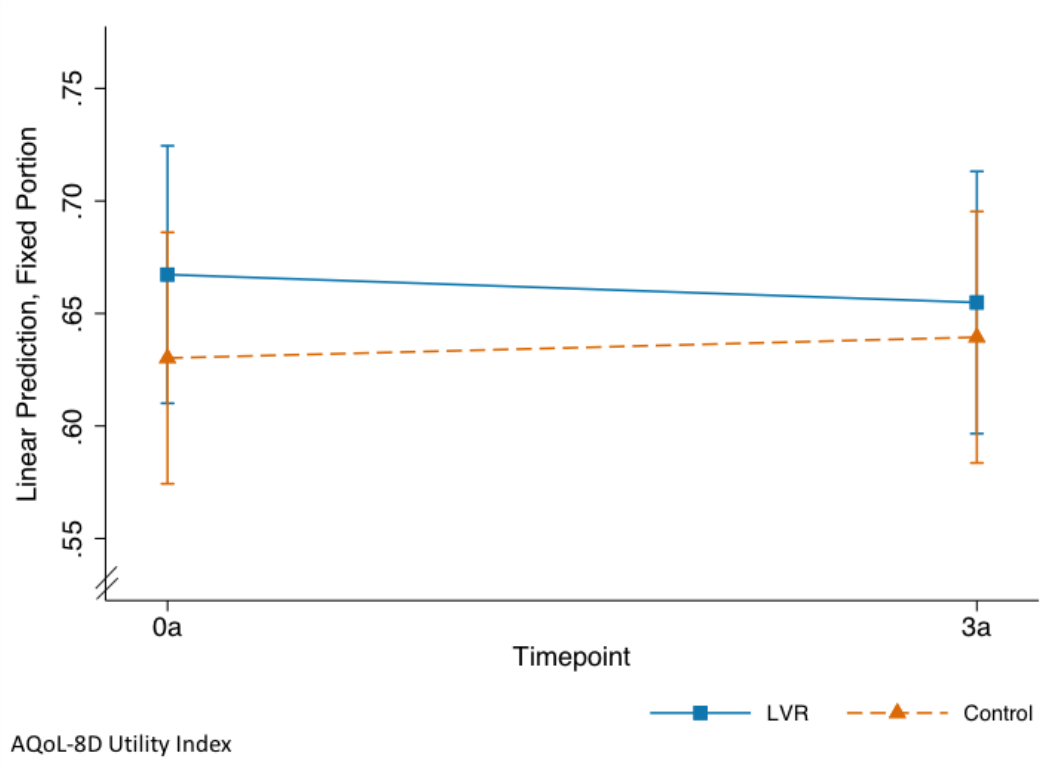

Figure 11-15: Linear mixed model of the AQoL-8D utility index, for the whole cohort. *Model not significant and no main effects or interaction.*

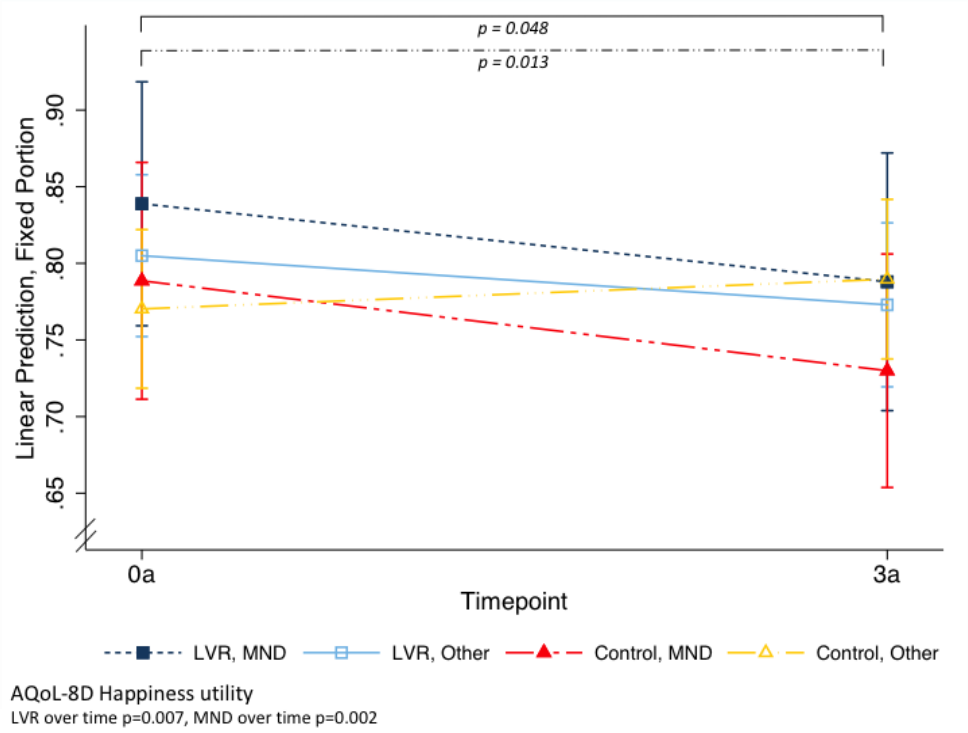

Figure 11-16: Linear mixed model of the AQoL-8D Happiness dimension of health state utility, by disease type. Model significant and main effect of time, disease by time interaction present.

11.5.5 SIDE EFFECTS & HOSPITAL PRESENTATIONS

	Musculoskeletal	Dizziness	SOB	Other	Total side effects
MND, LVR	1	1	0	2	4
Other NMD, LVR	4	5	2	0	11
Total LVR	**5**	**6**	**2**	**2**	**15**
MND, Control	0	0	2	0	2
Other NMD, Control	4	2	2	0	8
Total Control	**4**	**2**	**4**	**0**	**10**

Table 11-19: Side effects reported by participants, categorised by theme

LVR = lung volume recruitment, Control = active control, MND = motor neurone disease, Other NMD = other neuromuscular disease, SOB = shortness of breath. Number of participants reporting side effects: LVR group = 13 / 37, Control group = 9 / 39 (i.e., three participants reported two different side effects over the three-month trial).

	RTI Primary care presentation	RTI Hospital presentation	Hospital not RTI related	Total presentations
MND, LVR	1	0	3	4
Other NMD, LVR	2	1	2	5
Total LVR	**3**	**1**	**5**	**9**
MND, Control	0	0	3	3
Other NMD, Control	4	1	0	5
Total Control	**4**	**1**	**3**	**8**

Table 11-20: Primary care and hospital presentations, by treatment and disease

RTI Primary care presentation = primary-care / general practitioner diagnosed respiratory tract infection and antibiotic prescription; RTI Hospital presentation = Hospital admission for respiratory tract infection, Hospital not RTI related = Hospital admission for non-respiratory reasons.
LVR = lung volume recruitment, Control = active control, MND = motor neurone disease, Other NMD = other neuromuscular disease. Number of participants reporting any primary care or hospital presentation over the study duration: LVR group = 7 / 37, Control group = 8 / 39 (i.e., two LVR participants reported two separate hospital admissions for non-respiratory reasons).

11.5.6 IMMEDIATE EFFECT OF A SINGLE-SESSION OF LVR AFTER THREE-MONTHS

11.5.6.1 LINEAR MIXED MODELS BY DISEASE

Linear mixed models of the immediate effect of a single-session of LVR, by disease type (MND *vs.* Other NMD) were conducted in the non-naïve population at Timepoint 3. These repeat the analyses in Section 7.4.3, using Time 3b minus 3a.

	df	χ^2	*p*-value
LIC model: log restricted likelihood = -98.1		***17.6***	***0.0005***
Time	1	1.29	0.257
Disease	1	13.55	**0.0002**
Time*Disease	1	3.58	0.059
VC model = -46.2		***12.1***	***0.007***
Time	1	0.05	0.828
Disease	1	10.77	**0.001**
Time*Disease	1	1.27	0.261
LIC – VC model = -46.9		***12.1***	***0.031***
Time	1	1.55	0.214
Disease	1	1.95	0.162
Time*Disease	1	6.56	**0.010**
C_{rs} model = 333.9		***13.5***	***0.004***
Time	1	1.02	0.312
Disease	1	12.61	**0.0004**
Time*Disease	1	0.56	0.454
Specific C_{rs} model = 234.8		*3.7*	*0.302*
Time	1	0.95	0.329
Disease	1	1.79	0.181
Time*Disease	1	1.53	0.216
FRC model = -52.4		***47.5***	***< 0.0001***
Time	1	19.55	**<0.0001**
Disease	1	24.84	**<0.0001**
Time*Disease	1	13.90	**0.0002**
TLC model = -74.3		***33.4***	***< 0.0001***
Time	1	8.72	**0.003**
Disease	1	23.55	**<0.0001**
Time*Disease	1	4.44	**0.035**

	df	χ^2	*p*-value
RV model = -31.6		***25.5***	***< 0.0001***
Time	1	4.28	**0.039**
Disease	1	20.17	**<0.0001**
Time*Disease	1	1.55	0.213
PCF model = -685.4		***11.1***	***0.011***
Time	1	7.34	**0.007**
Disease	1	0.29	0.592
Time*Disease	1	0.18	0.675
PCF_{LIC} model = -684.1		*1.0*	*0.794*
Time	1	0.53	0.465
Disease	1	0.43	0.512
Time*Disease	1	0.04	0.833
PCF_{LIC} – PCF model = -661.9		*2.8*	*0.425*
Time	1	0.95	0.330
Disease	1	0.01	0.910
Time*Disease	1	0.58	0.448

Table 11-21: Linear mixed models of effect of i) Time and Disease on respiratory function in participants with neuromuscular disease, not naïve to lung volume recruitment (LVR), where Time represents pre and post a single-session of LVR, and Disease represents MND or Other NMD.

11.5.6.2 LINEAR MIXED MODELS BY DISEASE AND TREATMENT GROUP

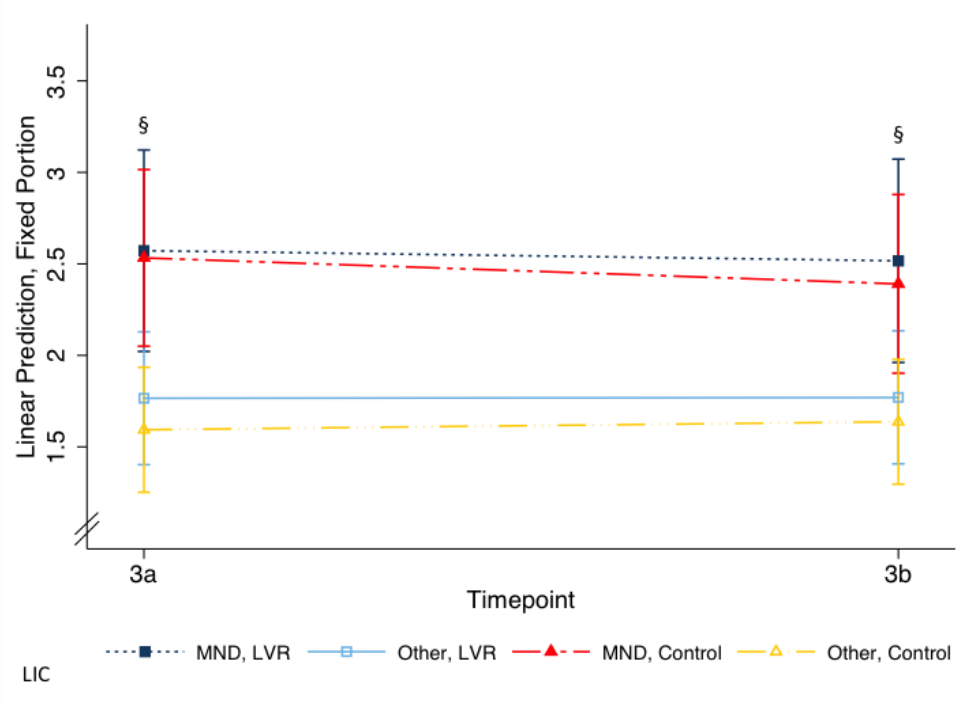

Figure 11-17: Linear mixed model of lung insufflation capacity (LIC), by disease type and treatment. Model significant and main effect of disease present.

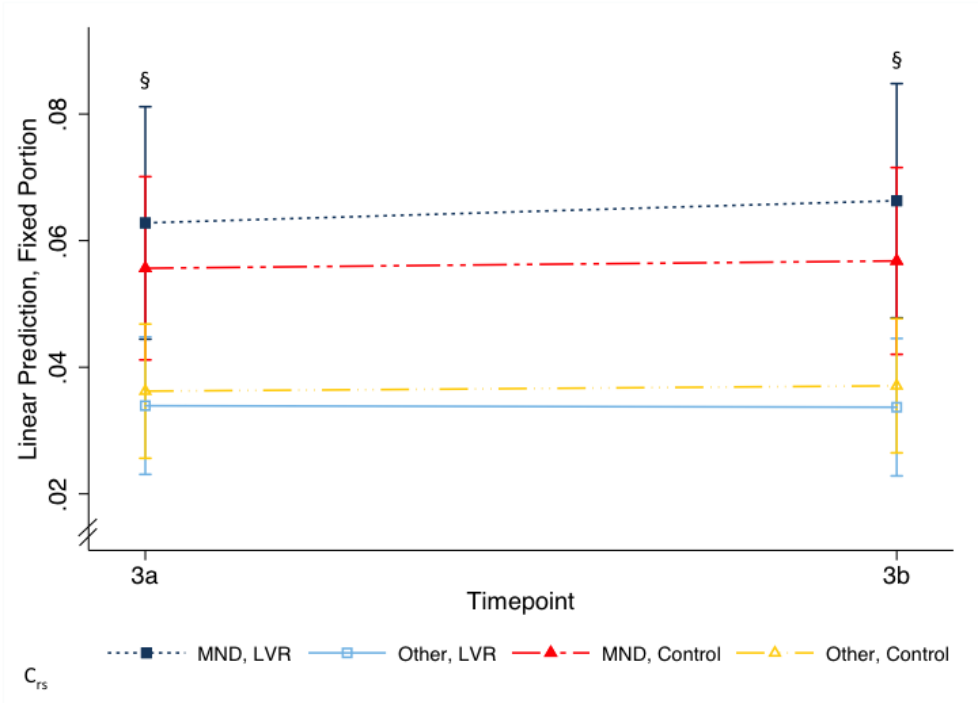

Figure 11-18: Linear mixed model of respiratory system compliance (C_{rs}), by disease type and treatment. Model significant and main effect of disease present.

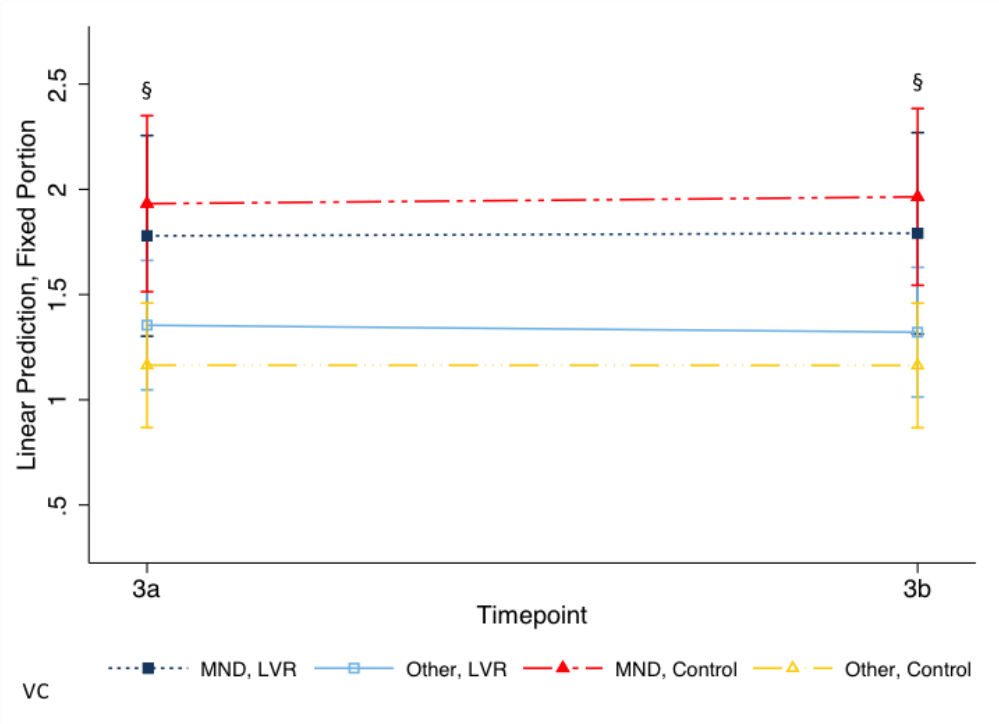

Figure 11-19: Linear mixed model of vital capacity (VC), by disease type and treatment. Model not significant but main effect of disease present.

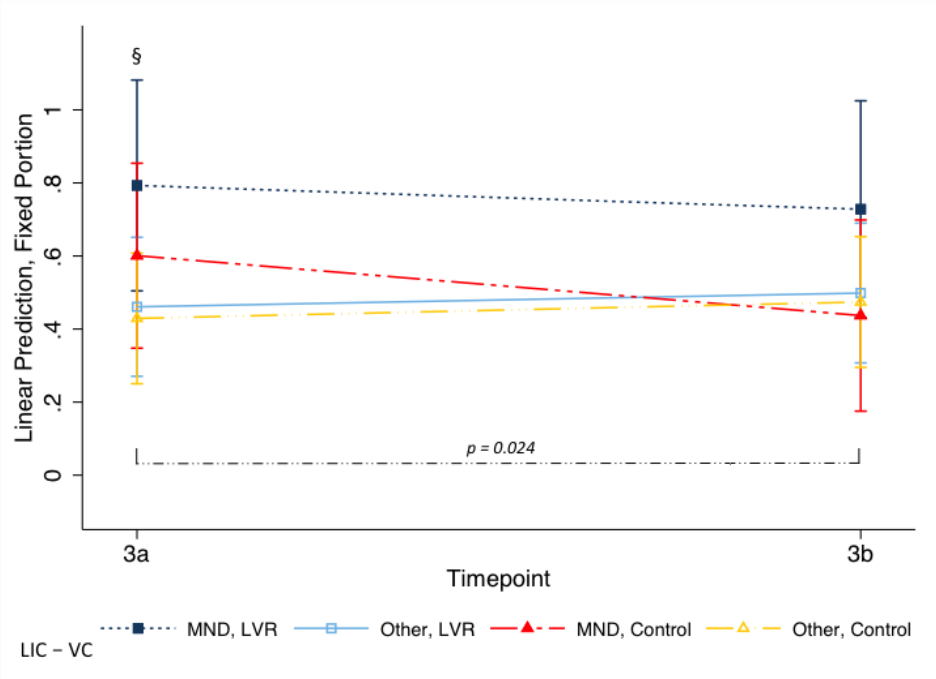

Figure 11-20: Linear mixed model of lung insufflation capacity minus vital capacity (LIC – VC), by disease type and treatment. Model not significant but time by disease interaction present.

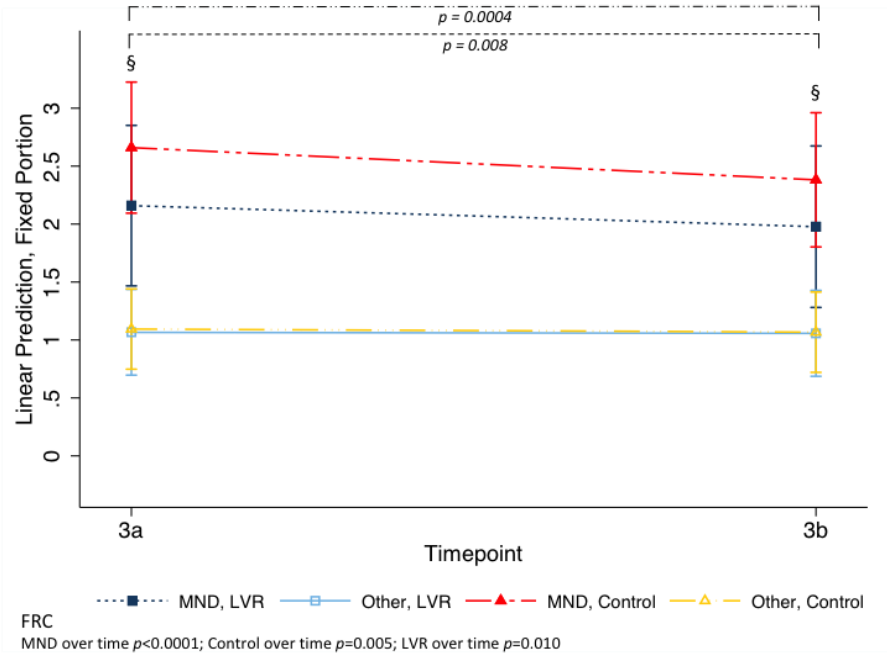

Figure 11-21: Linear mixed model of functional residual capacity (FRC), by disease type and treatment. Model significant, main effects of time, disease and a time by disease interaction present.

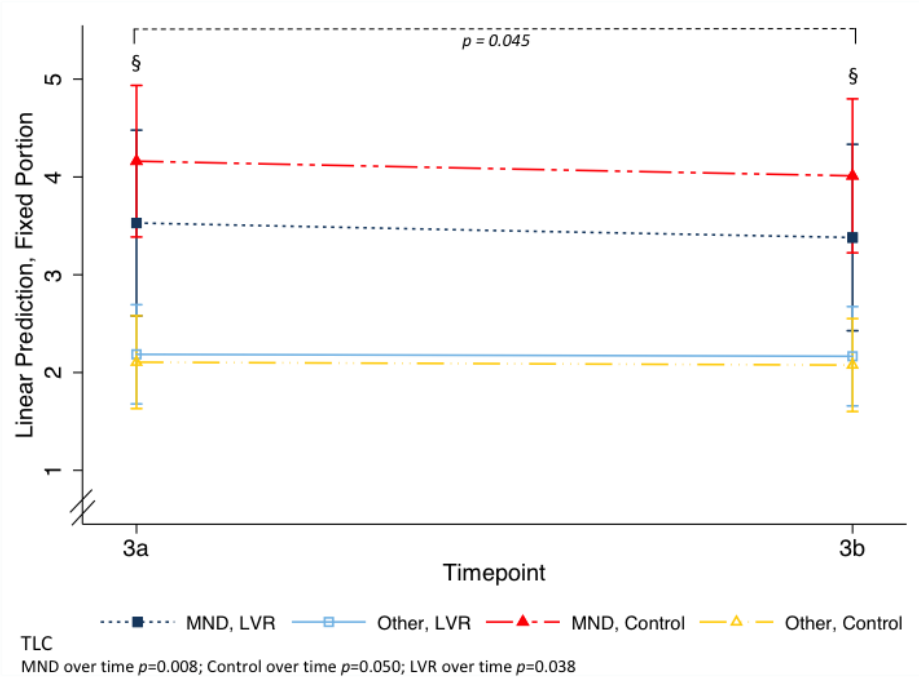

Figure 11-22: Linear mixed model of total lung capacity (TLC), by disease type and treatment. Model significant, main effects of time, disease and a time by disease interaction present.

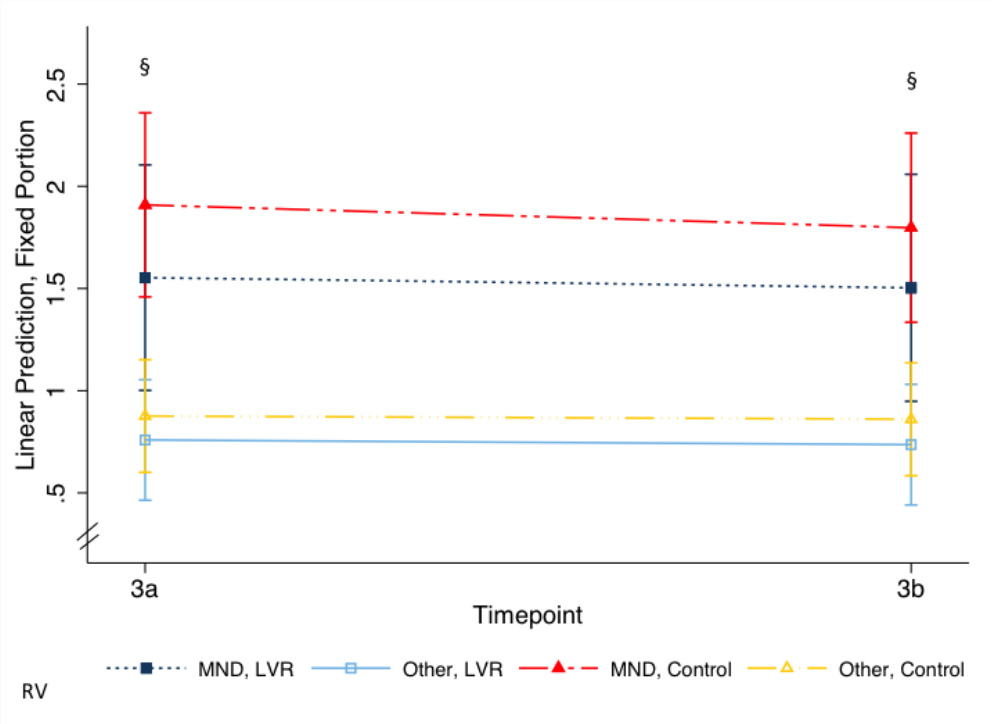

Figure 11-23: Linear mixed model of residual volume (RV), by disease type and treatment. Model significant, main effects of time and disease present.

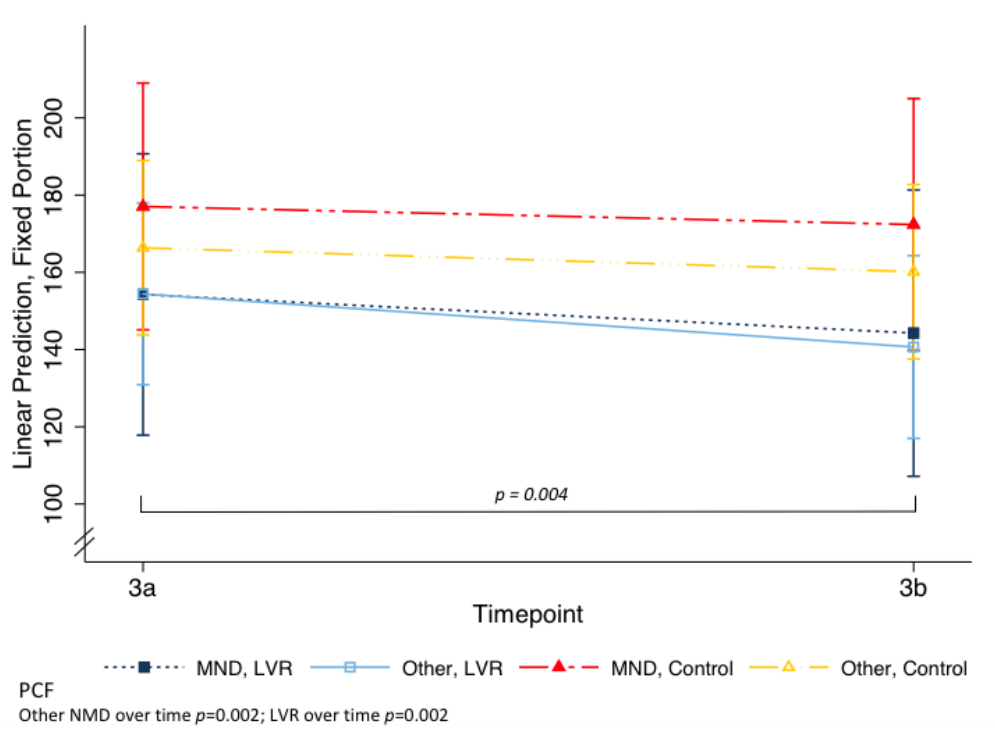

Figure 11-24: Linear mixed model of peak cough flow (PCF), by disease type and treatment. Model significant and main effect of time present.

11.5.7 IMMEDIATE EFFECTS OF LVR AT 3-MONTHS: POST-HOC COMPARISON BY TREATMENT GROUP AND DISEASE SUB-GROUPS

The following tables represent the observed mean difference (95% confidence interval) in each respiratory variable, across time and between treatment and disease sub-groups.

For each table: (n) = number of participants; Time = Timepoint; LVR = lung volume recruitment group; Control = active control group; MND = motor neurone disease group, Other = Other neuromuscular disease group. Shaded cells refer to comparisons that were statistically significant in the linear mixed models. *P*-values in bold indicate statistically significant values ($p<0.05$).

LIC (L)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3b – 3a	30 : 36	-0.01	-0.13	0.12	0.916
Between disease type over time						
MND *vs.* Other	Δ Time 3b – 3a	18 : 48	-0.14	-0.27	0.00	**0.048**
Within group over time						
Time 3b - 3a	**LVR**	30	-0.02	-0.12	0.08	0.741
Time 3b - 3a	MND, LVR	8	-0.07	-0.36	0.23	0.602
Time 3b - 3a	Other, LVR	22	0.00	-0.10	0.11	0.955
Time 3b - 3a	**Control**	36	-0.01	-0.09	0.07	0.820
Time 3b - 3a	MND, Control	10	-0.15	-0.40	0.10	0.214
Time 3b - 3a	Other, Control	26	0.04	-0.03	0.11	0.209
Time 3b - 3a	**MND**	18	-0.11	-0.28	0.06	0.182
Time 3b - 3a	**Other**	48	0.03	-0.03	0.08	0.394

Table 11-22: Post-hoc comparisons of immediate effects on LIC

VC (L)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3b – 3a	30 : 36	-0.03	-0.09	0.03	0.334
Between disease type over time						
MND *vs.* Other	Δ Time 3b – 3a	18 : 48	0.04	-0.03	0.11	0.286
Within group over time						
Time 3b - 3a	**LVR**	30	-0.02	-0.07	0.02	0.332
Time 3b - 3a	MND, LVR	8	0.01	-0.10	0.12	0.853
Time 3b - 3a	Other, LVR	22	-0.03	-0.09	0.02	0.208
Time 3b - 3a	**Control**	36	0.01	-0.04	0.05	0.701
Time 3b - 3a	MND, Control	10	0.03	-0.08	0.14	0.524
Time 3b - 3a	Other, Control	26	0.00	-0.05	0.05	0.974
Time 3b - 3a	**MND**	18	0.02	-0.05	0.09	0.517
Time 3b - 3a	**Other**	48	-0.02	-0.05	0.02	0.373

Table 11-23: Post-hoc comparisons of immediate effects on VC

LIC – VC (L)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3b – 3a	30 : 36	0.02	-0.10	0.14	0.695
Between disease type over time						
MND *vs.* Other	Δ Time 3b – 3a	18 : 48	-0.18	-0.30	-0.05	**0.007**
Within group over time						
Time 3b - 3a	**LVR**	30	0.01	-0.08	0.10	0.897
Time 3b - 3a	MND, LVR	8	-0.08	-0.33	0.18	0.496
Time 3b - 3a	Other, LVR	22	0.04	-0.06	0.13	0.435
Time 3b - 3a	**Control**	36	-0.02	-0.10	0.06	0.662
Time 3b - 3a	MND, Control	10	-0.18	-0.38	0.02	0.070
Time 3b - 3a	Other, Control	26	0.04	-0.04	0.13	0.263
Time 3b - 3a	**MND**	18	-0.13	-0.28	0.01	0.062
Time 3b - 3a	**Other**	48	0.04	-0.02	0.10	0.171

Table 11-24: Post-hoc comparisons of immediate effects on LIC – VC

C_{rs} (L/cmH_2O)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3b – 3a	28 : 32	-0.0004	-0.0049	0.0041	0.846
Between disease type over time						
MND *vs.* Other	Δ Time 3b – 3a	15 : 45	0.0021	-0.0030	0.0073	0.413
Within group over time						
Time 3b - 3a	**LVR**	28	0.0006	-0.0022	0.0033	0.676
Time 3b - 3a	MND, LVR	7	0.0034	-0.0032	0.0101	0.254
Time 3b - 3a	Other, LVR	21	-0.0004	-0.0036	0.0028	0.808
Time 3b - 3a	**Control**	32	0.0010	-0.0025	0.0046	0.566
Time 3b - 3a	MND, Control	8	0.0015	-0.0041	0.0071	0.545
Time 3b - 3a	Other, Control	24	0.0008	-0.0037	0.0054	0.705
Time 3b - 3a	**MND**	15	0.0024	-0.0013	0.0061	0.190
Time 3b - 3a	**Other**	45	0.0003	-0.0025	0.0030	0.842

Table 11-25: Post-hoc comparisons of immediate effects on C_{rs}

Specific C_{rs} (L/cmH_2O/L)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3b – 3a	22 : 24	-0.0006	-0.0069	0.0058	0.861
Between disease type over time						
MND *vs.* Other	Δ Time 3b – 3a	7 : 39	0.0054	-0.0033	0.0141	0.219
Within group over time						
Time 3b - 3a	**LVR**	22	0.0001	-0.0053	0.0054	0.983
Time 3b - 3a	MND, LVR	4	0.0031	-0.0022	0.0084	0.161
Time 3b - 3a	Other, LVR	18	-0.0006	-0.0072	0.0059	0.844
Time 3b - 3a	**Control**	24	0.0006	-0.0033	0.0046	0.751
Time 3b - 3a	MND, Control	3	0.0073	-0.0102	0.0249	0.214
Time 3b - 3a	Other, Control	21	-0.0003	-0.0046	0.0039	0.867
Time 3b - 3a	**MND**	7	0.0049	0.0001	0.0097	**0.048**
Time 3b - 3a	**Other**	45	-0.0005	-0.0041	0.0031	0.792

Table 11-26: Post-hoc comparisons of immediate effects on Specific C_{rs}

FRC (L)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3b – 3a	23 : 25	0.02	-0.07	0.11	0.714
Between disease type over time						
MND *vs.* Other	Δ Time 3b – 3a	7 : 41	-0.21	-0.32	-0.10	**0.0004**
Within group over time						
Time 3b - 3a	**LVR**	23	-0.04	-0.11	0.03	0.232
Time 3b - 3a	MND, LVR	4	-0.19	-0.57	0.19	0.213
Time 3b - 3a	Other, LVR	19	-0.01	-0.07	0.05	0.731
Time 3b - 3a	**Control**	25	-0.06	-0.12	0.00	0.065
Time 3b - 3a	MND, Control	3	-0.28	-0.81	0.24	0.145
Time 3b - 3a	Other, Control	22	-0.03	-0.08	0.02	0.281
Time 3b - 3a	**MND**	7	-0.23	-0.43	-0.03	**0.030**
Time 3b - 3a	**Other**	41	-0.02	-0.06	0.02	0.311

Table 11-27: Post-hoc comparisons of immediate effects on FRC

TLC (L)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3b – 3a	23 : 25	0.00	-0.09	0.09	0.984
Between disease type over time						
MND *vs.* Other	Δ Time 3b – 3a	7 : 41	-0.13	-0.25	-0.01	**0.034**
Within group over time						
Time 3b - 3a	**LVR**	23	-0.04	-0.12	0.03	0.244
Time 3b - 3a	MND, LVR	4	-0.15	-0.39	0.08	0.131
Time 3b - 3a	Other, LVR	19	-0.02	-0.10	0.06	0.616
Time 3b - 3a	**Control**	25	-0.04	-0.10	0.01	0.099
Time 3b - 3a	MND, Control	3	-0.16	-0.53	0.22	0.212
Time 3b - 3a	Other, Control	22	-0.03	-0.08	0.03	0.277
Time 3b - 3a	**MND**	7	-0.16	-0.28	-0.03	**0.024**
Time 3b - 3a	**Other**	41	-0.03	-0.07	0.02	0.281

Table 11-28: Post-hoc comparisons of immediate effects on TLC

RV (L)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3b – 3a	23 : 25	0.00	-0.07	0.07	0.974
Between disease type over time						
MND *vs.* Other	Δ Time 3b – 3a	7 : 41	-0.06	-0.16	0.03	0.192
Within group over time						
Time 3b - 3a	**LVR**	23	-0.03	-0.08	0.03	0.289
Time 3b - 3a	MND, LVR	4	-0.05	-0.38	0.27	0.632
Time 3b - 3a	Other, LVR	19	-0.02	-0.08	0.03	0.375
Time 3b - 3a	**Control**	25	-0.03	-0.07	0.02	0.201
Time 3b - 3a	MND, Control	3	-0.12	-0.43	0.19	0.246
Time 3b - 3a	Other, Control	22	-0.02	-0.06	0.03	0.474
Time 3b - 3a	**MND**	7	-0.08	-0.23	0.07	0.239
Time 3b - 3a	**Other**	41	-0.02	-0.05	0.01	0.246

Table 11-29: Post-hoc comparisons of immediate effects on RV

PCF (L/min)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3b – 3a	30 : 36	-7.1	-18.0	3.8	0.197
Between disease type over time						
MND *vs.* Other	Δ Time 3b – 3a	18 : 48	1.8	-10.6	14.1	0.775
Within group over time						
Time 3b - 3a	**LVR**	30	-13.0	-19.0	-7.1	**0.0001**
Time 3b - 3a	MND, LVR	8	-11.3	-18.4	-4.1	**0.007**
Time 3b - 3a	Other, LVR	22	-13.7	-21.6	-5.7	**0.002**
Time 3b - 3a	**Control**	36	-5.9	-14.8	2.9	0.184
Time 3b - 3a	MND, Control	10	-5.1	-24.8	14.6	0.570
Time 3b - 3a	Other, Control	26	-6.2	-16.8	4.7	0.238
Time 3b - 3a	**MND**	18	-7.9	-18.3	2.6	0.131
Time 3b - 3a	**Other**	48	-9.6	-16.3	-3.0	**0.005**

Table 11-30: Post-hoc comparisons of immediate effects on PCF

PCF_{LIC} (L/min)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3b – 3a	30 : 35	-4.0	-17.7	9.7	0.564
Between disease type over time						
MND *vs.* Other	Δ Time 3b – 3a	17 : 48	-2.5	-18.1	13.1	0.753
Within group over time						
Time 3b - 3a	**LVR**	30	-4.9	-17.1	7.3	0.415
Time 3b - 3a	MND, LVR	8	3.5	-21.3	28.4	0.747
Time 3b - 3a	Other, LVR	22	-8.0	-23.0	7.0	0.279
Time 3b - 3a	**Control**	35	-0.9	-8.6	6.8	0.806
Time 3b - 3a	MND, Control	9	-11.8	-30.7	7.0	0.185
Time 3b - 3a	Other, Control	26	2.8	-5.6	11.3	0.495
Time 3b - 3a	**MND**	17	-4.6	-18.7	9.5	0.498
Time 3b - 3a	**Other**	48	-2.1	-10.2	5.9	0.597

Table 11-31: Post-hoc comparisons of immediate effects on PCF_{LIC}

PCF_{LIC} – PCF (L/min)		n	Mean difference	95% CI		*p*-value
Between-group over time						
LVR *vs.* Control	Δ Time 3b – 3a	30 : 35	3.7	-11.9	19.3	0.633
Between disease type over time						
MND *vs.* Other	Δ Time 3b – 3a	17 : 48	-5.4	-23.1	12.3	0.546
Within group over time						
Time 3b - 3a	**LVR**	30	8.1	-3.8	20.0	0.175
Time 3b - 3a	MND, LVR	8	14.8	-7.7	37.3	0.165
Time 3b - 3a	Other, LVR	22	5.7	-9.3	20.7	0.439
Time 3b - 3a	**Control**	35	4.4	-6.2	15.0	0.409
Time 3b - 3a	MND, Control	9	-9.1	-24.5	6.3	0.208
Time 3b - 3a	Other, Control	26	9.0	-4.2	22.3	0.173
Time 3b - 3a	**MND**	17	2.1	-11.2	15.4	0.739
Time 3b - 3a	**Other**	48	7.5	-2.1	17.1	0.122

Table 11-32: Post-hoc comparisons of immediate effects on PCF_{LIC} – PCF difference

11.5.8 Immediate Effect of a Single-Session of LVR: Comparison between Change at Baseline and Change at Final Assessment

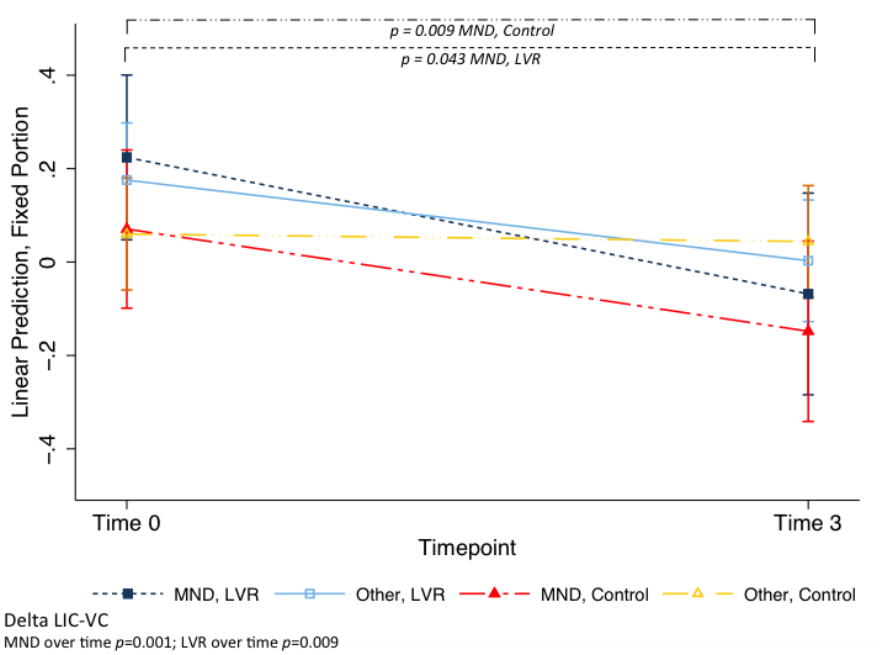

Figure 11-25: Linear mixed model of the immediate response in lung insufflation capacity minus vital capacity difference (change in LIC-VC post- minus pre- a single-session of LVR, Delta LIC-VC), by disease type and treatment. Model significant and main effect of time present.

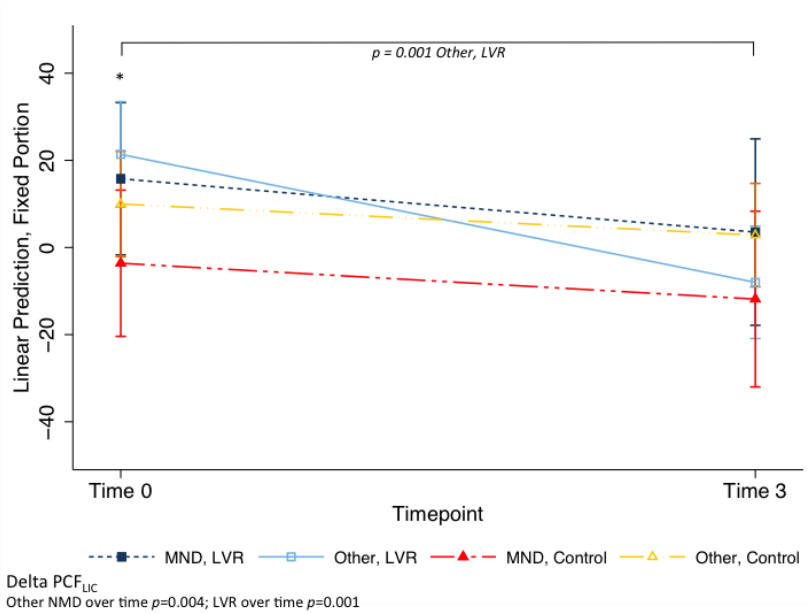

Figure 11-26: Linear mixed model of the immediate peak cough flow from lung insufflation capacity response (change in PCF_{LIC} post- minus pre- a single-session of LVR, Delta PCF_{LIC}), by disease type and treatment. Model significant and main effect of time present.

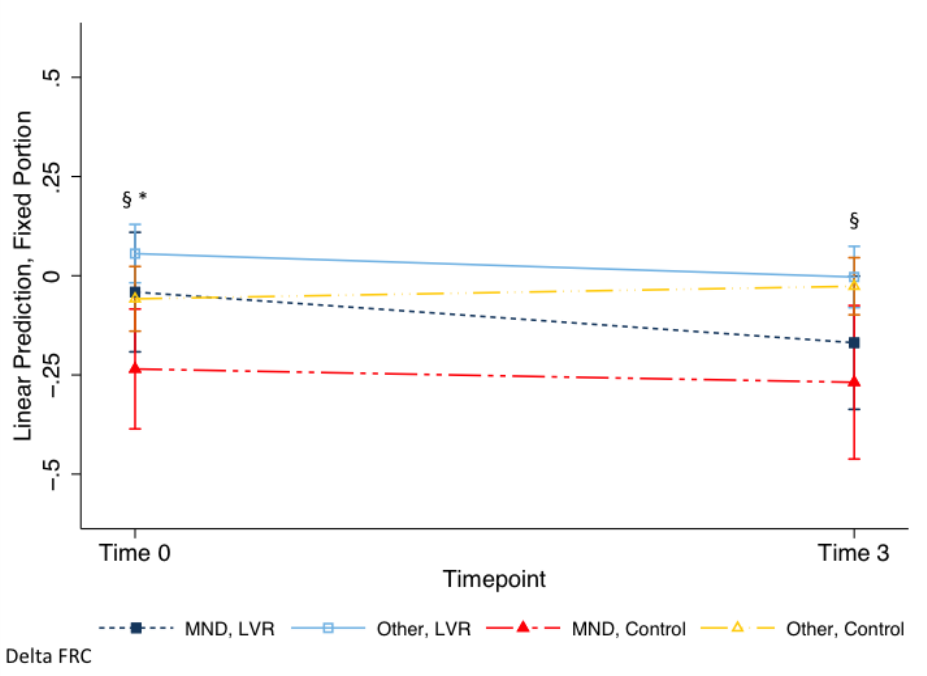

Figure 11-27: Linear mixed model of the immediate functional residual capacity response (change in FRC post- minus pre- a single-session of LVR, Delta FRC), by disease type and treatment. Model significant and main effects of treatment and disease present.

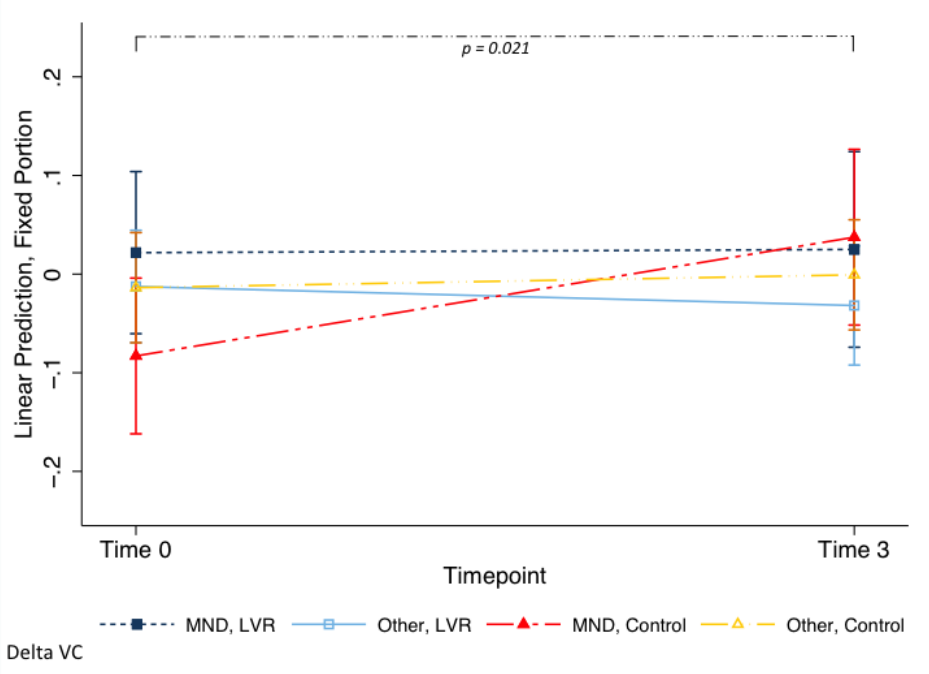

Figure 11-28: Linear mixed model of the immediate vital capacity response (change in VC post- minus pre- a single-session of LVR, Delta VC), by disease type and treatment. Model not significant and no main effects present.

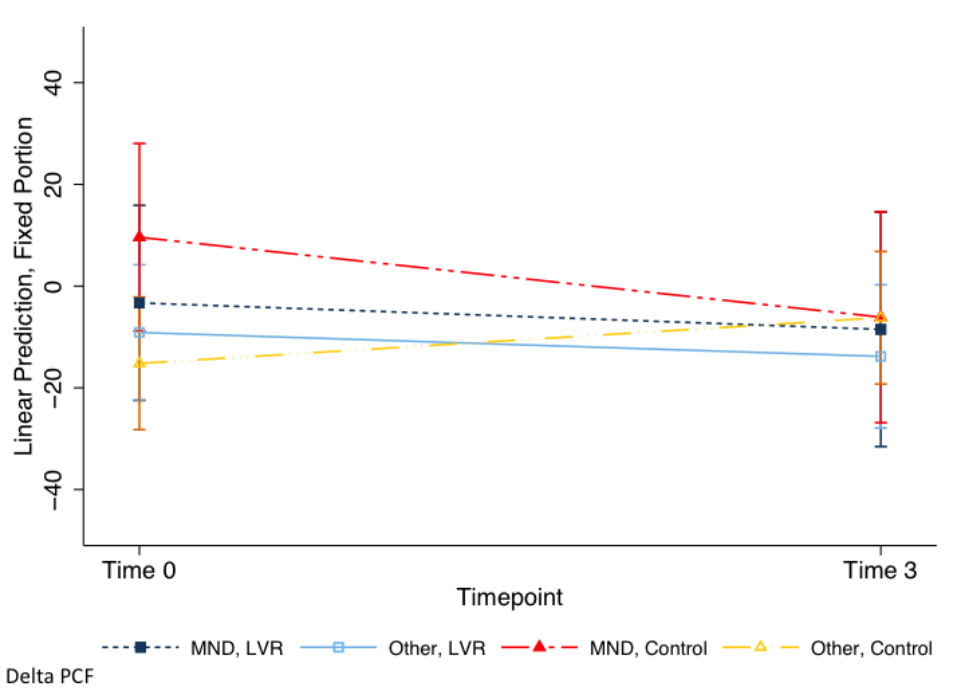

Figure 11-29: Linear mixed model of the immediate peak cough flow response (change in PCF post- minus pre- a single-session of LVR, Delta PCF), by disease type and treatment. Model not significant and no main effects present.

11.5.9 Exploratory Analyses of Associations Between Changes in Respiratory Function

The following graphs illustrate the relationship between change in LIC and other respiratory function variables, where:

Data represent individual participant change over time values (where delta = Timepoint 3a minus 0a). LIC = lung insufflation capacity (litres); LVR = lung volume recruitment group; Control = active control group; MND = motor neurone disease; Other = other neuromuscular diseases including chest wall disease. Pearson's r refers to the LVR and Control groups (all analyses non-statistically significant).

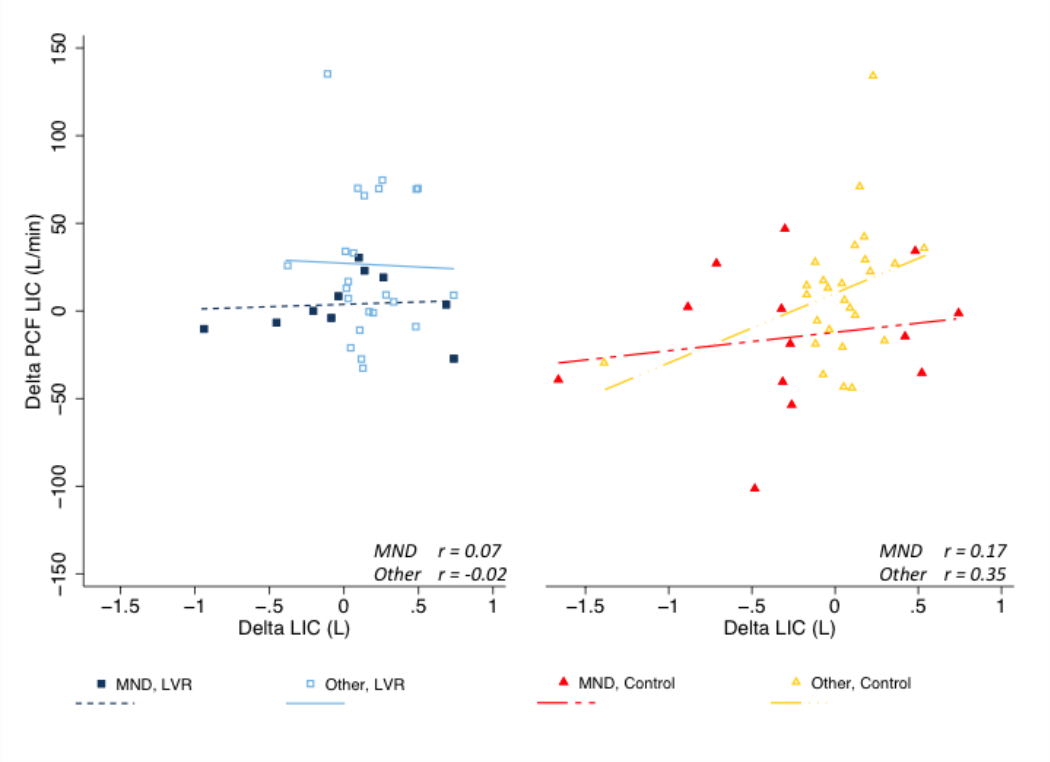

Figure 11-30: Relationship between change in LIC and change in PCF_{LIC}, by treatment

Markers represent individual participant change over time values (delta = Timepoint 3a minus 0a); lines represent the line of best fit.

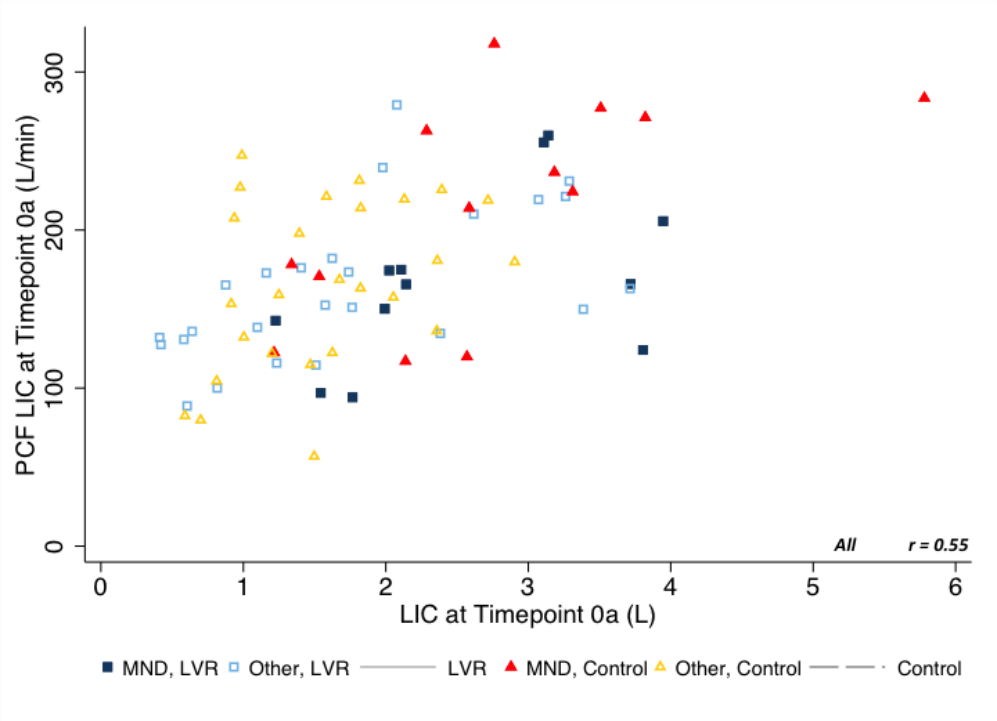

Figure 11-31: Relationship between LIC and PCF_{LIC} values at Timepoint 0a

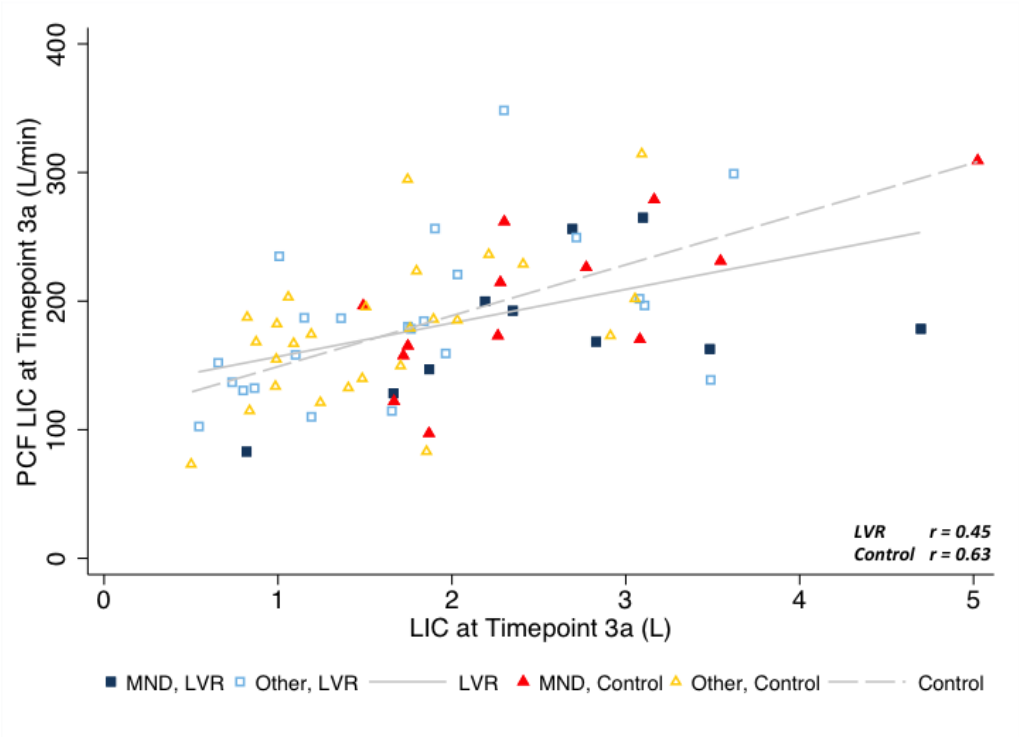

Figure 11-32: Relationship between LIC and PCF_{LIC} values at Timepoint 3a

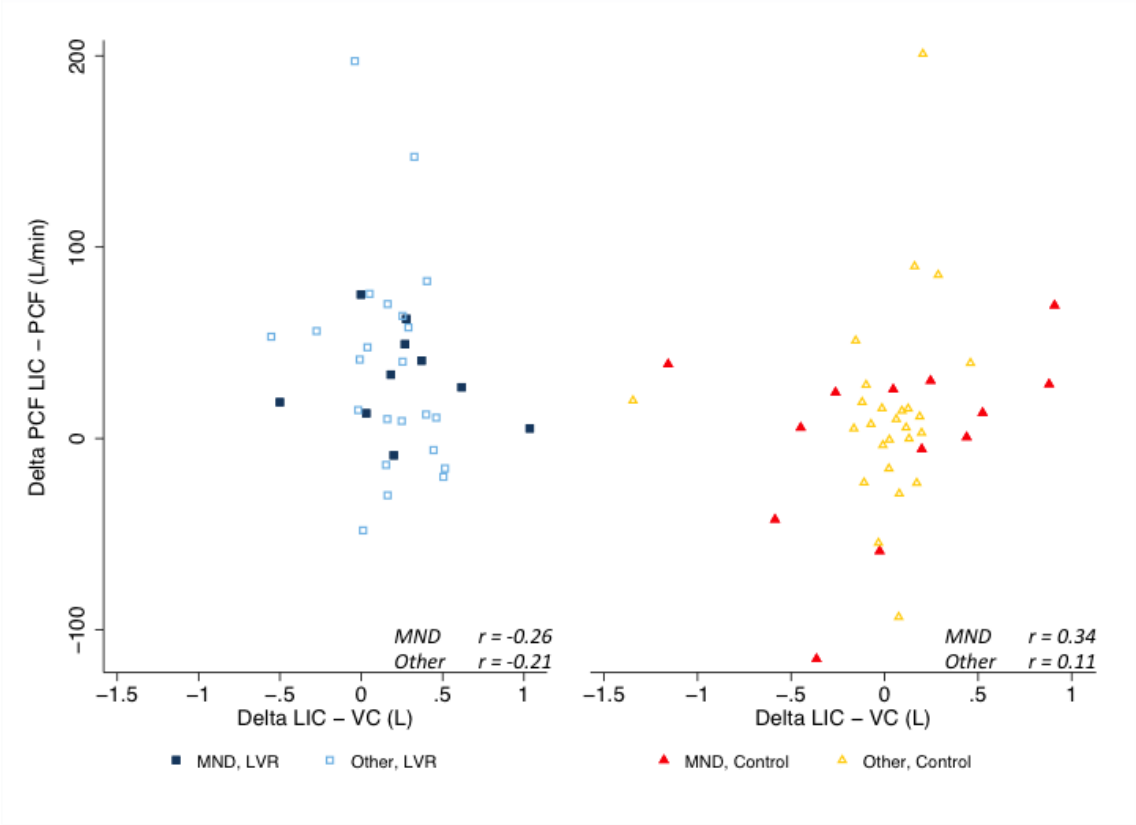

Figure 11-33: Relationship between change in LIC – VC and change in PCF_{LIC} – PCF, by treatment

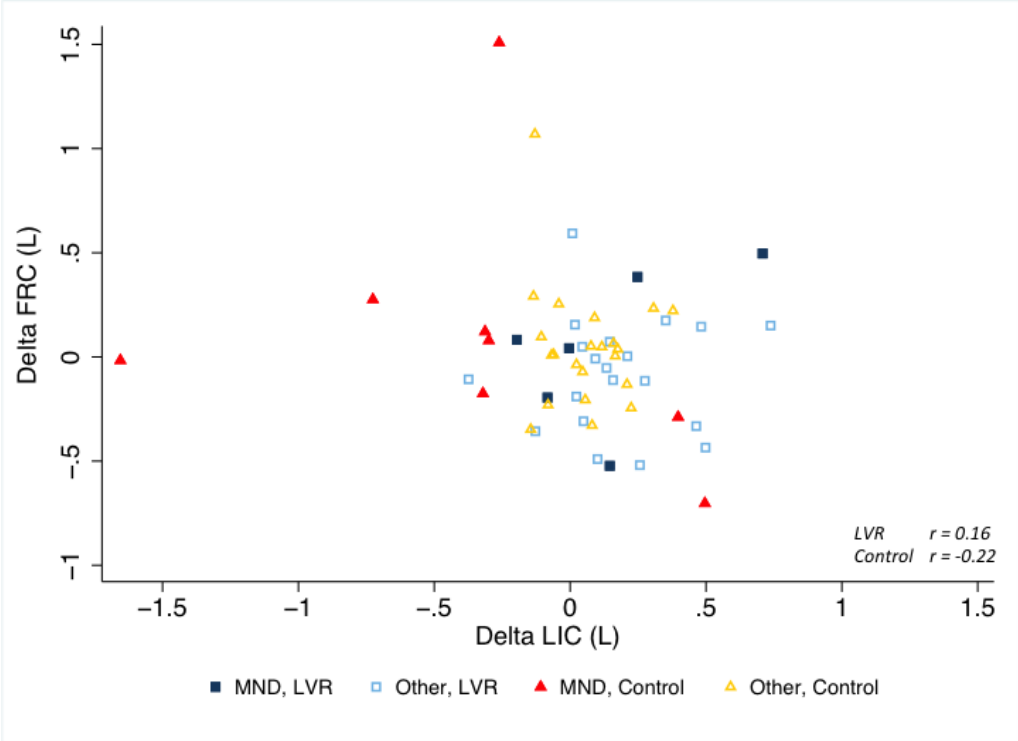

Figure 11-34: Relationship between change in LIC and change in FRC

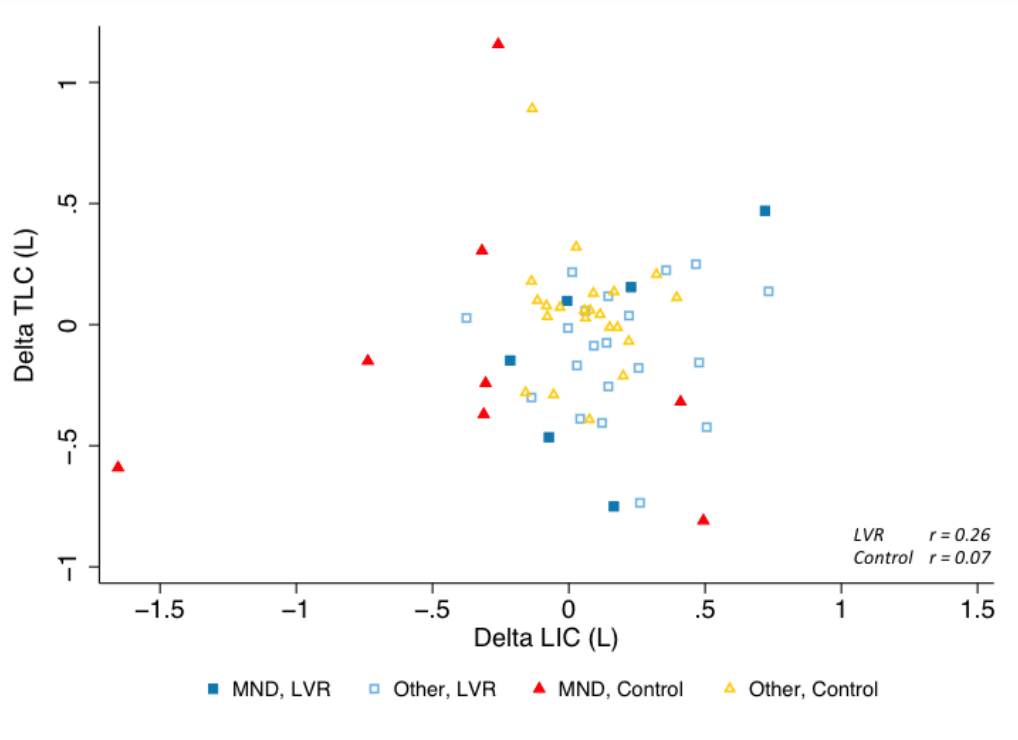

Figure 11-35: Relationship between change in LIC and change in TLC

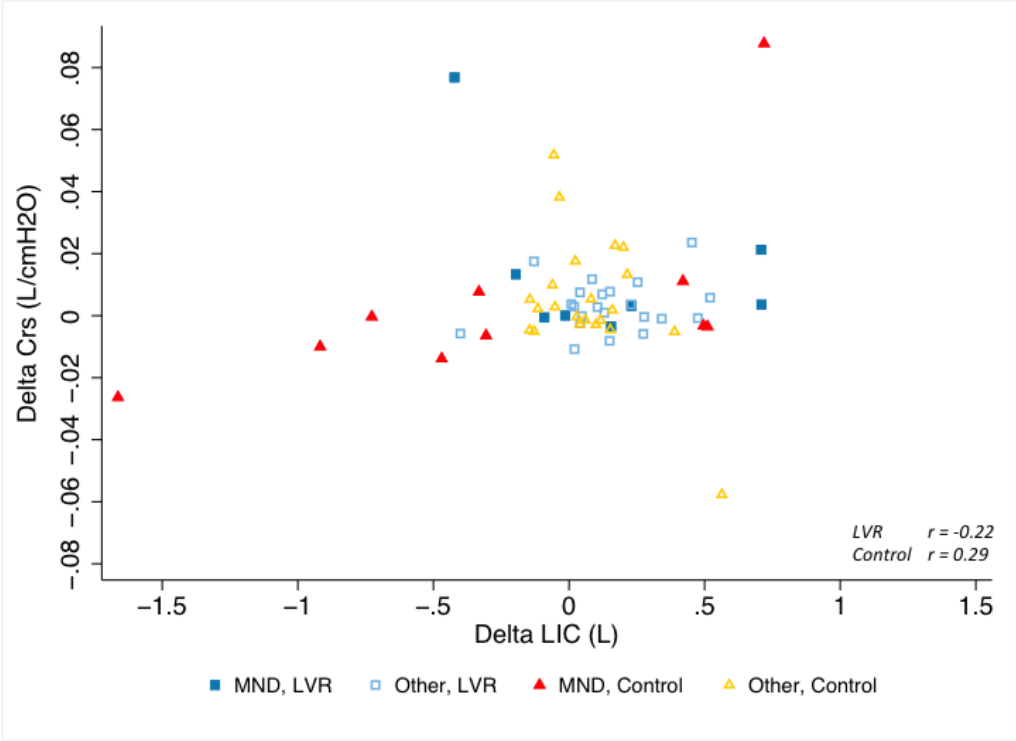

Figure 11-36: Relationship between change in LIC and change in C_{rs}