Rapidly and slowly progressive neuromuscular disease: differences in pulmonary function, respiratory tract infections and response to lung volume recruitment therapy (LVR)

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ABSTRACT

Introduction Reduced lung volumes are a hallmark of respiratory muscle weakness in neuromuscular disease (NMD). Low respiratory system compliance (C_{rs}) may contribute to restriction and be amenable to lung volume recruitment (LVR) therapy. This study evaluated respiratory function and the immediate impact of LVR in rapidly progressive compared to slowly progressive NMD.

Methods We compared vital capacity (VC), static lung volumes, maximal inspiratory and expiratory pressures (MIP, MEP), C_{rs} and peak cough flow (PCF) in 80 adult participants with motor neuron disease ('MND'=27) and more slowly progressive NMDs ('other NMD'=53), pre and post a single session of LVR. Relationships between respiratory markers and a history of respiratory tract infections (RTI) were examined.

Results Participants with other NMD had lower lung volumes and C_{rs} but similar reduction in respiratory muscle strength compared with participants with MND (VC=1.30±0.77 vs 2.12±0.75 L, p<0.001; C_{rs}=0.0331±0.0245 vs 0.0473±0.0241 L/cmH$_2$0, p=0.024; MIP=39.8±21.3 vs 37.8±19.5 cmH$_2$0). More participants with other NMD reported an RTI in the previous year (53% vs 22%, p=0.01). The likelihood of having a prior RTI was associated with baseline VC (%predicted) (OR=1.03 (95% CI 1.00 to 1.06), p=0.029). Published thresholds (VC<1.1 L or PCF<270 L/min) were, however, not associated with prior RTI.

A single session of LVR improved C_{rs} (mean (95% CI) increase = 0.0038 (0.0001 to 0.0075) L/cmH$_2$0, *p*=0.047) but not VC.

Conclusion These findings corroborate the hypothesis that ventilatory restriction in NMD is related to weakness initially with respiratory system stiffness potentiating lung volume loss in slowly progressive disease. A single session of LVR can improve C_{rs}. A randomised controlled trial of regular LVR is needed to assess longer-term effects.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ People with neuromuscular disease (NMD) have respiratory muscle weakness and low lung volumes. Reduced respiratory system compliance (C_{rs}) may also be a factor and may be amenable to lung volume recruitment (LVR).

WHAT THIS STUDY ADDS

⇒ Reduced C_{rs} is a characteristic of respiratory dysfunction, particularly in slowly progressive, long-standing NMD. A single session of LVR can improve C_{rs}

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports the clinical and biological rationale for regular LVR in people with NMD, and highlights the need for a randomised controlled trial of daily LVR therapy.

(NMD). As diseases progress and lung volumes decline, people lose the ability to inspire and cough effectively, resulting in hypercapnia, respiratory failure and consideration for home mechanical ventilation.[1] Ultimately, most people die of respiratory complications.[2] Reduced vital capacity (VC) reflects inspiratory and expiratory respiratory muscle weakness, however, lung volume loss is greater than that expected for the degree of muscle weakness alone. Studies conducted 30–50 years ago in small samples of participants with slowly progressive NMDs suggest that lower lung (C_L), chest wall (C_{CW}) or total respiratory system compliance (C_{rs}) may contribute to ventilatory restriction, although the exact mechanisms remain elusive.[3–5] Poor lung function is also hypothesised to increase respiratory tract infection (RTI) risk and

INTRODUCTION

Restrictive ventilatory impairment is a hallmark of most neuromuscular diseases

rate,[6] however, there is limited literature regarding the incidence of RTI in NMD, associations with lung function, and any differences between people with recent compared with long-standing weakness.

Clinical guidelines recommend daily lung volume recruitment (LVR) therapy, based on the hypothesis that regular assisted inflation may counter lung volume decline.[7 8] A modified bagging circuit (LVR kit) or the mechanical inflation component of a mechanical insufflator-exsufflator (MI-E) are two methods available. However, studies evaluating the physiological effect of LVR on respiratory outcomes are few,[9 10] and none compare the effects in different types of NMD.

The primary aims of this study were to evaluate (1) the relationships between respiratory function, lung volumes, C_{rs}, respiratory muscle strength and peak cough flow (PCF); (2) the relationship between respiratory function and a history of an RTI and (3) the immediate physiological effect of a single session of LVR on C_{rs} in people with NMD naïve to the technique. The secondary aims were to explore whether there were differences in these relationships between those with recent (ie, amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)) vs long-standing, slowly progressive weakness (Other NMD).

METHODS
Study design
A prospective study evaluating baseline characteristics and the immediate effect of a single session of LVR was conducted (ACTRN12615000565549). Recruitment was via three specialist state-wide providers in Victoria, Australia: the adult home mechanical ventilation service, adult progressive neurological disease service and the paediatric neuromuscular service. Potential participants were identified by treating clinicians at routine outpatient clinic or by searching the ventilation service's clinical database. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research project; public and patient review of research is provided through membership of the local human research ethics committee.

Participants
Patients >14 years old with NMD or restrictive chest wall disease (>3 months postdiagnosis) and a forced VC <80% of predicted normal[11] were eligible. Participants were categorised a priori into disease subgroups based on rapidity of disease progression (MND or other NMDs).

Exclusion criteria were: daily LVR or assisted inflation therapy for more than six consecutive weeks within the past 6 months, acute respiratory inpatient admission within the preceding 6 weeks, contraindications or precautions for positive pressure therapy, medical instability, invasive ventilation or non-proficiency in English. Non-invasive ventilation (NIV) users needed to be on therapy for >3 months. All participants gave informed consent.

Procedure
Demographic data, ventilation use, self-reported history of an RTI requiring antibiotic treatment within the previous 12 months, measures of respiratory function and the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R)[12] (MND subgroup only) were collected ('Baseline').

Respiratory function tests were performed seated without a seatbelt or abdominal binder, according to taskforce statements.[13–15] Two acceptable and reproducible trials were taken if fatigue prevented three trials.[16] Testing order was standardised: slow VC, unassisted PCF ('biggest, strongest' cough into an oro-nasal mask),[6] C_{rs} (pulse inflation method),[10 17] static lung volumes (functional residual capacity (FRC), total lung capacity (TLC), residual volume (RV), inspiratory capacity (IC), expiratory reserve volume (ERV)), maximal inspiratory and expiratory pressures sustained at the mouth for 1 s (maximal inspiratory pressure (MIP) from RV, maximal expiratory pressure (MEP) from TLC), sniff nasal inspiratory pressure (SNIP), lung insufflation capacity[6] (LIC) and PCF from LIC (PCF_{LIC}). Outcomes were expressed in absolute values, percentage of predicted normal (%pn)[11 18 19] and z-scores[11] where available. Equipment specifications and detailed methods are provided in online supplemental file.

Following the Baseline assessment, participants rested for 45 min before performing a single session of LVR therapy (details in figure 1). Respiratory function testing was repeated immediately after the LVR intervention ('post-LVR'), excluding MIP, MEP and SNIP.

Statistical analysis
These data formed the baseline assessment of a randomised controlled trial (RCT) (ACTRN12615000565549), with the sample size calculation based on that needed to detect a between-group difference in the RCT's primary outcome. Data are presented as mean±SD, median (IQR) or frequencies (percentage) as appropriate. Baseline respiratory function was compared with (1) disease and (2) a history of RTI as subgroups, using Student's independent t-tests, Fisher's exact test for proportions or the Mann-Whitney U-statistic for non-parametric data as appropriate. To investigate which variables contributed towards lung volume for the disease types (MND, other NMD), a multivariate forward stepwise regression model was constructed using explanatory variables that correlated with VC (z-score; to control for age, height and sex) at p≤0.10 on univariate analysis. Stepwise logistic regression modelling examined relationships between a history of RTI, disease and respiratory function. Based on clinically important thresholds for care escalation cited in practice standards,[6 7 20–22] receiver operating characteristic (ROC) curves were used to assess the ability of a PCF<270 L/min[23] or a VC<1.1 L[24] to correctly classify participants who had a past RTI episode or not.
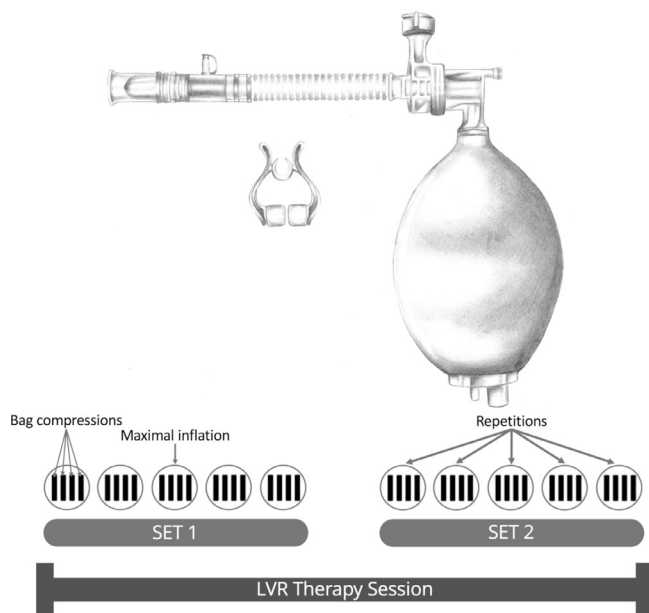
Figure 1 Single session of lung volume recruitment (LVR) therapy: LVR kit and dose. LVR kit comprising a self-inflating 1.6 L manual resuscitation bag, tubing, one-way in-line valve, mouthpiece and nose clip (item number 1034502; Mercury Medical; Florida, USA) (or oro-nasal mask if lip seal was not maintained). The standardised dose comprised two sets of five maximal inflations (repetitions). The number of bag compressions required to reach the maximum, tolerable insufflation capacity and hence achieve one maximal inflation was titrated to each individual, based on chest wall excursion and participant comfort. Original artwork illustrated by KS.

Linear mixed models with time, disease (fixed effects) and participant (random effect) investigated the effect of a single session of LVR on respiratory function. Post hoc comparisons of within-group change and between-group change over time employed paired and independent Student's t-tests respectively (mean effect (95% CI)). Analyses were performed using Stata/IC V.15.1 for Mac (StataCorp); p values<0.05 were considered statistically significant.

RESULTS
Between 2 September 2015 and 21 May 2019, 80 consecutive participants (age range 18.0–85.8 years) with NMD were recruited and underwent Baseline assessment (figure 2, table 1).

Respiratory function
Participants had severely reduced lung volumes and weak respiratory muscles (group mean±SD VC = 41%±19%pn, TLC=45%±17 %pn, MIP=44%±26%pn, MEP=42%±22%pn). VC and lung volumes were significantly higher in people with MND, whether expressed as an absolute value or standardised for age, sex and height. No differences in the relative contribution of IC, ERV, RV or FRC to TLC; nor MIP, MEP, SNIP or PCF were

observed between disease groups (table 2). Total C_{rs} and LIC were higher in those with MND compared with other NMDs. The LIC–VC difference was not significantly different between disease groups (expressed as absolute difference or change from VC).

Multivariate modelling found that MEP was associated with VC in participants with MND with the fitted regression equation: VC (z-score)=−4.29 + 0.03*MEP (R^2=0.37, $F(1,15)$=8.77, p=0.010). In participants with Other NMDs, C_{rs} and MEP were related to VC where: VC (z-score)=−7.53 + 0.03*MEP+34.77* C_{rs} (R^2=0.36, $F(2,41)$=11.69, p<0.001).

Respiratory tract infections
In the year prior to study enrolment 34 participants (43%), predominantly those with Other NMDs (53% vs 22%, p=0.01), reported at least one RTI; an overall incidence of 0.60 episodes/participant/year. Participants reporting an RTI had lower mean VC, FRC, RV, TLC and PCF values, although static lung volumes were not different when expressed relative to TLC (table 3). Despite lower mean VC and PCF values in the RTI group (figure 3), VC (L) and PCF (L/min) were poor at distinguishing a history of RTI (AUC (95% CI) for VC=0.64 (0.52 to 0.77), PCF=0.65 (0.52 to 0.77); online supplemental figure S6). Applying published thresholds of VC<1.1 L[24] and PCF<270 L/min[23] to this cohort correctly classified 61% and 50% of participants, respectively, as having a prior RTI (sensitivity and specificity VC=44% and 74%; PCF=97% and 15%).

In the logistic regression model, the only factor associated with having a history of RTI was VC(%pn) with each 1% increase in VC associated with a 3% improvement in the likelihood of not having an RTI (model log likelihood=−39.8, χ^2=4.8, p=0.029; OR=1.03 (95% CI 1.00 to 1.06)).

Immediate effect of LVR
Statistically significant changes over time were found on linear model analyses for C_{rs}, LIC, PCF_{LIC}, FRC and TLC (online supplemental table S1). A mean improvement in the primary outcome of C_{rs} of 0.0038 (0.0001, 0.0075) L/cmH$_2$O was observed (table 4), with post hoc analysis suggesting this was largely attributable to change within the MND disease group (MND=0.0115 (0.0014, 0.0216) L/cmH$_2$O, p=0.029; Other NMD=0.0006 (-0.0025, 0.0038) L/cmH$_2$O, p=0.688; figure 4).

The improvements in LIC and PCF_{LIC} observed after LVR (table 4) did not differ between disease groups (LIC between-group mean difference=0.04 (−0.13, 0.21) L, p=0.670; PCF_{LIC}=−7.4 (−24.1, 9.3) L/min, p=0.380). Reductions in FRC and TLC over time demonstrated on linear modelling (online supplemental table S1) were not apparent on post hoc comparisons of observed effects (table 4).
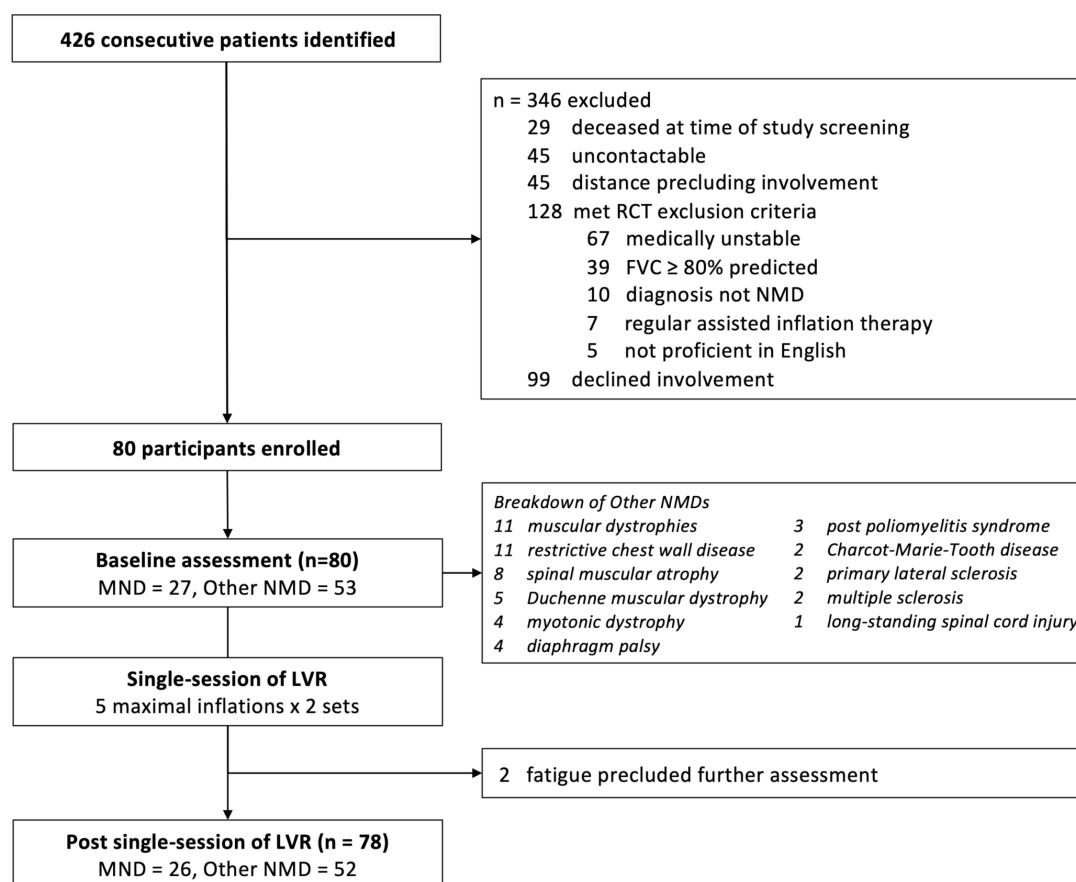
Figure 2 Participant flow. FVC, forced vital capacity; LVR, lung vol recruitment; MND, motor neuron disease; NMD, neuromuscular diseases; RCT, randomised controlled trial.

DISCUSSION

This study measured comprehensive respiratory function in a cohort of 80 community-dwelling people with NMD and respiratory system involvement, with 78 participants repeating testing immediately post a single session of LVR therapy. We found that people with MND had

Table 1	Demographic data, for the cohort as a whole and by disease subgroup			
	All (n=80)	**MND (n=27)**	**Other NMD (n=53)**	**P value**
Age (years)	59.2 (31.8–68.0)	65.9 (59.2–71.2)	48.7 (27.0–65.1)	**<0.001**
Sex (male)	44 (55%)	19 (70%)	25 (47%)	**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)	**<0.001**
Time since symptom onset (years)	14.4 (2.2–25.5)	1.9 (1.2–3.0)	22.6 (15.4–44.2)	**<0.001**
NIV user (yes)	62 (78%)	20 (74%)	42 (79%)	0.600
Gastrostomy (yes)	21 (26%)	17 (63%)	4 (8%)	**<0.001**
Self-reported RTI in past year (yes)	34 (43%)	6 (22%)	28 (53%)	**0.010**
ALSFRS-R		24.2±7.6		
ALSFRS-R bulbar subscore ≤9[39]		12 (44%)		

Data are presented as mean±SD, median (lower–upper quartile) or count (percentage).
Bulbar subscore ≤9 indicates moderate bulbar symptoms as per Smith *et al*.[39]
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).
ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; BMI, body mass index; MND, motor neuron disease; NIV, non-invasive ventilation; NMD, neuromuscular disease; RTI, respiratory tract infection.

Table 2 Respiratory function at baseline, for the cohort as a whole and by disease subgroup

Variable	MND		Other NMD		P value
VC (L) (%pn)	2.12±0.75 (53)	27	1.30±0.77 (35)	53	**<0.001**
VC (z-score)	−3.25±1.32	27	−5.22±1.85	53	**<0.001**
PCF (L/min)	187.4±61.3	27	171.9±72.6	53	0.346
MIP (cmH$_2$O) (%pn)	37.8±19.5 (39)	25	39.8±21.3 (47)	52	0.693
MEP (cmH$_2$O) (%pn)	50.8±27.1 (40)	21	48.7±26.4 (44)	48	0.767
SNIP (cmH$_2$O) (%pn)	22.5±9.5 (24)	26	27.7±15.2 (29)	52	0.119
C_{rs} (L/cmH$_2$O)	0.0473±0.0241	23	0.0331±0.0245	49	**0.024**
IC (L)	1.59±0.58	19	1.10±0.62	44	**0.004**
ERV (L)	0.62±0.44	19	0.29±0.20	44	**<0.001**
FRC (L) (%pn)	2.10±1.10 (62)	19	1.09±0.64 (37)	44	**<0.001**
RV (L) (%pn)	1.48±0.71 (63)	19	0.80±0.55 (48)	44	**<0.001**
TLC (L) (%pn)	3.69±1.48 (57)	19	2.19±1.04 (40)	44	**<0.001**
IC % TLC	44.2±9.6	19	50.4±15.1	44	0.103
ERV % TLC	15.3±7.1	19	13.3±6.0	44	0.268
RV % TLC (%pn)	40.5±8.4 (104)	19	36.1±16.4 (115)	44	0.269
FRC % TLC (%pn)	55.8±9.6 (99)	19	49.4±15.0 (94)	44	0.093
LIC (L)	2.62±1.05	27	1.65±0.83	53	**<0.001**
LIC–VC (L)	0.49±0.66	27	0.35±0.44	53	0.233
LIC–VC (%VC)	26.0±32.4	27	39.5±52.0	53	0.222
PCF$_{LIC}$ (L/min)	191.7±65.3	27	166.4±50.2	53	0.059
PCF$_{LIC}$ – PCF (L/min)	4.3±42.3	27	−5.5±56.3	53	0.429

Data are presented as mean±SD (mean per cent predicted) and 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 subgroups; data in bold indicate statistically significant values (p<0.05).

C_{rs}, respiratory system compliance; ERV, expiratory reserve volume; FRC, functional residual capacity; IC, inspiratory capacity; LIC, lung insufflation capacity; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MND, motor neuron disease; Other NMD, other neuromuscular diseases; PCF, Peak cough flow; PCF$_{LIC}$, PCF from LIC; RV, residual volume; SNIP, sniff nasal inspiratory pressure; TLC, total lung capacity; VC, vital capacity; volume % TLC, lung vol variable expressed as a percentage of absolute TLC.

better preserved lung volumes than participants with other NMDs for similar reduction in respiratory muscle strength, suggesting that factors other than weakness contribute to ventilatory restriction. This latter subgroup had been living with weakness for ~20 years more than those with MND and had lower C_{rs} indicating respiratory system 'stiffness'. Participants with other NMD had smaller absolute static lung volumes (IC, ERV, FRC, RV, TLC), however, when compartments were expressed as a percentage of TLC no between-group difference was observed. This suggests lower lung volumes overall, rather than a selective reduction in IC as has previously been suggested.[5 25 26] We observed a group mean decrease in RV, whereas other authors have reported normal RV,[3 10 26] or wide-ranging FRC and ERV values.[27] The large variance in static lung volumes observed herein and by others may reflect small sample sizes and heterogeneity in which particular respiratory muscles are affected.

It has previously been observed that lung volume loss in people with slowly progressive NMD is more than that expected for the degree of muscle weakness alone, with reduced lung distensibility secondary to microatelectasis, and/or changes in the elastic properties of the lungs and/or chest wall thought to play a role.[3–5 25 28] Studies were small (≤25 participants), conducted in an era prior to optimised medical management and domiciliary NIV (which may prevent chest wall restriction), and thus may not represent contemporary populations. More recently, a study of 12 people with slowly progressive NMD found a relationship between VC and C_{rs} (r=0.65, p<0.05).[10] Our study is the largest to-date to demonstrate that respiratory system stiffness is a characteristic of slowly progressive, long-standing NMD.

However, it has not been established whether reduced C_{rs} is a factor in rapidly progressive disease, as previous research has not included the effect of the chest wall. In a study of 14 participants with MND, C_L was lower than healthy participants,[29] however, this could be a product of their smaller lung volumes. Dynamic C_L was not different in 26 participants compared with healthy controls, and remained stable in the 11 people with MND with 6-month follow-up data.[30] It is therefore unclear whether the elastic

Table 3 Respiratory function at baseline, by a history of respiratory tract infection

Variable	No RTI		RTI		Mean difference (95% CI)	P value
MND: Other NMD (count)	21 : 25		6 : 28			
VC (L)	1.75±0.83	46	1.35±0.84	34	0.40 (0.02 to 0.77)	**0.039**
VC (%pn)	45.6±17.4	46	35.1±18.7	34	10.5 (2.4 to 18.6)	**0.012**
VC (z-score)	−4.07±1.78	46	−5.22±1.95	34	1.15 (0.31 to 1.98)	**0.008**
PCF (L/min)	192.9±77.5	46	155.7±48.9	34	37.2 (7.0 to 67.3)	**0.016**
MIP (%pn)	42.3±24.3	43	47.3±27.5	34	−5.0 (−16.7 to 6.8)	0.403
MEP (%pn)	41.8±18.9	37	43.0±25.3	32	−1.2(−11.8 to 9.5)	0.824
SNIP (%pn)	28.5±15.6	44	26.6±13.6	34	1.9 (−4.8 to 8.6)	0.571
C_{rs} (L/cmH$_2$O)	0.0394±0.0230	41	0.0354±0.0280	31	0.0039 (−0.0080 to 0.0159)	0.513
IC (L)	1.37±0.64	34	1.10±0.63	29	0.28 (−0.04 to 0.60)	0.088
ERV (L)	0.43±0.37	34	0.33±0.27	29	0.10 (−0.07 to 0.27)	0.237
FRC (%pn)	52.0±28.4	34	36.6±18.7	29	15.4 (3.0 to 27.8)	**0.015**
RV (%pn)	61.3±38.9	34	43.0±24.3	29	18.4 (1.7 to 35.0)	**0.032**
TLC (%pn)	50.8±16.7	34	38.7±14.6	29	12.0 (4.1 to 20.0)	**0.004**
FRC % TLC	52.8±12.5	34	49.7±15.4	29	3.1 (−4.0 to 10.1)	0.386
RV % TLC	39.3±13.8	34	35.2±15.3	29	4.1 (−3.3 to 11.4)	0.273

Data are presented as mean±SD, followed by 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 subgroups; data in bold indicate statistically significant values (p<0.05).
No RTI=no episode of self-reported respiratory tract infection in the preceding 12 months. Other=Other neuromuscular disease, RV=Residual volume,
C_{rs}, respiratory system compliance; ERV, expiratory reserve volume; FRC, functional residual capacity; IC, inspiratory capacity; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MND, motor neuron disease; PCF, peak cough flow; RTI, respiratory tract infection; SNIP, sniff nasal inspiratory pressure; TLC, total lung capacity; VC, vital capacity.

property of lung parenchyma is affected in a rapid adult-onset disease. The current C_{rs} data comprise both C_{CW} and C_L, and provide the first insights in MND. Our values from 23 participants suggest lower C_{rs} than published healthy control data using the same technique (figure 4) but higher C_{rs} than the subgroup with long-standing other NMDs, indicating that in MND there is a mild degree of 'stiffness' present in the respiratory system.

A novel aspect of this study is the between disease-group comparison of respiratory impairment. Our observation that lung volume is lower for similar weakness in the slowly progressive Other NMD subgroup, corroborates the hypothesis that ventilatory restriction in NMD is related to weakness initially, with chest wall and/or lung tissue stiffness potentiating lung volume loss over time.[3 5 28] Furthermore, as illustrated by the regression models, respiratory muscle strength contributed to larger VC in all participants but in those with more long-standing NMD an additional influence of C_{rs} was observed, with higher C_{rs} values associated with better lung volume. A longitudinal study involving respiratory volumes, strength and compliance measurements from childhood across the decades is needed to confirm this hypothesis.

Understanding the mechanisms contributing to lung volume loss and trying to prevent decline is important in NMD, as poor lung volumes are related to clinical outcomes such as need for domiciliary ventilation and survival.[1] Moreover, reduced lung volume and an ineffective cough are thought to increase the risk of developing acute respiratory compromise or RTI.[6 24]
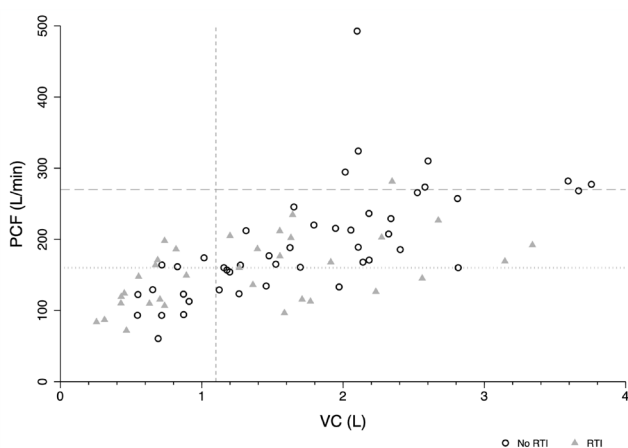

Figure 3 Vital capacity (L) and peak cough flow (PCF) (L/min), by a history of respiratory tract infection. Dotted reference line indicates PCF value of 160 L/min, dashed reference line indicates PCF value of 270 L/min, vertical reference line indicates VC of 1.1 L, as per published data[23 24 40] and incorporated into NMD management guidelines.[6 7 20–22] NMD, neuromuscular disease; RTI, respiratory tract infection; VC, vital capacity.

Table 4 Respiratory function at baseline and post a single session of lung volume recruitment

Variable	N	Baseline	Post-LVR	Observed mean difference (95% CI)	P value
C_{rs} (L/cmH$_2$O)	65	0.0377±0.0258	0.0415±0.0270	0.0038 (0.0001 to 0.0075)	**0.047**
LIC (L)	78	1.99±1.02	2.12±1.07	0.13 (0.05 to 0.21)	**0.002**
VC (L)	78	1.57±0.86	1.54±0.84	−0.03 (−0.07 to 0.01)	0.142
LIC–VC (L)	78	0.42±0.50	0.57±0.43	9.4 (2.9 to 15.8)	**0.0003**
LIC–VC (%VC)	78	36.5±45.9	45.9±43.8	0.16 (0.07 to 0.24)	**0.005**
FRC (L)	49	1.39±0.98	1.36±0.97	−0.03 (−0.09 to 0.03)	0.348
TLC (L)	49	2.64±1.45	2.60±1.41	−0.03 (−0.10 to 0.03)	0.266
RV (L)	49	1.00±0.73	0.99±0.71	−0.02 (−0.07 to 0.04)	0.610
ERV (L)	49	0.38±0.32	0.37±0.34	−0.01 (−0.05 to 0.02)	0.435
IC (L)	49	1.24±0.70	1.25±0.67	0.00 (−0.04 to 0.04)	0.890
PCF (L/min)	78	175.5±69.1	169.9±57.6	−5.6 (−15.0 to 3.9)	0.244
PCF$_{LIC}$ (L/min)	77	174.8±56.7	186.4±57.9	11.6 (3.7 to 19.5)	**0.005**
PCF$_{LIC}$ – PCF	77	−1.5±51.9	15.7±39.5	17.2 (4.2 to 30.2)	**0.010**

Total number of participants who completed assessments at both time points=78. Data are presented as mean±SD and mean difference (95% CIs). (n)=the number of participants with technically acceptable measurements at both time points. Results were not obtainable in all due to bulbar impairment, technical issues or fatigue. P value represents paired t-test comparison; data in bold indicate statistically significant values (p<0.05).

C_{rs}, respiratory system compliance; ERV, expiratory reserve volume; FRC, functional residual capacity; IC, inspiratory capacity; LIC, lung insufflation capacity; LVR, lung volume recruitment; PCF, peak cough flow; PCF$_{LIC}$, PCF from LIC; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

The proportion of people with NMD who experience an RTI is imprecise; cross-sectional study values range from 9% to 75%[24 31–34] likely due to differences in study methodology, RTI definition, observation period, sampling source, recall and selection bias, among others. We observed a self-reported RTI rate over the preceding year of 43% of participants; an incidence of 0.60 RTI episodes/participant/year. This value is similar to other retrospective cohorts[24 31] and to a population-based data-linkage longitudinal study, which reported a respiratory admission rate of 0.47 episodes/participant/year across all NMD diagnoses.[35]

We observed lower lung volumes in participants with a history of RTI, and a greater proportion of participants with slowly progressive NMD (53%) compared with MND (22%) reported an RTI. VC was the only respiratory parameter associated with RTI: for every 1% increase in VC (%pred), the likelihood of avoiding an RTI over the past year improved by 3%. However, when the VC (<1.1 L[24]) and PCF (<270 L/min[23]) cut-offs that are interpreted as predicting risk of RTI were applied and ROC curves calculated, these threshold values poorly discriminated between participants who had self-reported an event or not (VC$_{sensitivity}$=44%, PCF$_{sensitivity}$=97%, VC$_{specificity}$=74%, PCF$_{specificity}$=15%). Over 90% of participants in our trial had a PCF lower than 270 L/min,[23] however, only 43% reported an RTI in the previous year, despite none performing regular airway clearance techniques (figure 3). Our findings highlight the discriminant imprecision of a single parameter to identify participants who have experienced an RTI.

The ability to predict patients at risk of developing an RTI and implement preventative management is highly desirable in diseases where respiratory complications are the primary cause of discomfort and death. Two studies by Sancho et al, in clinic samples comprising fewer than 40 people with ALS, observed that those with a PCF<255 L/
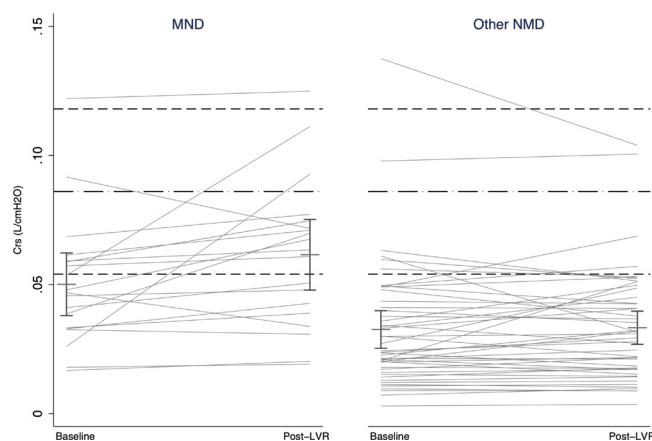

Figure 4 Respiratory system compliance (C_{rs}) at baseline and post a single session of lung volume recruitment in participants with MND (left) and Other NMDs (right). Markers represent group mean and 95% CI. Mean change in MND=0.0115 (0.0014, 0.0216) L/cmH$_2$O, p=0.029; Other NMD=0.0006 (−0.0025, 0.0038) L/cmH$_2$O, p=0.688; mean between-disease type difference 0.0038 (0.0030, 0.0187) L/cmH$_2$O, p=0.008. Dashed reference lines refer to mean (±2 SD) values from Suratt et al (healthy control data).[17] LVR, lung volume recruitment; MND, motor neuron disease; NMD, neuromuscular disease.

min had a clinically ineffective cough (unable to clear secretions) during an RTI[34] and those with a PCF<174L/min were more likely to need non-invasive ventilatory support during an RTI.[36] While these clinical studies provide useful information to guide care once a person with ALS has an RTI, there are no prospective data that actually predict a person's risk of developing an RTI or not, and provide associated predictor variables. Robust longitudinal data that incorporate broad risk factor assessment including respiratory and bulbar function, use of adjunctive respiratory therapies, NIV and artificial feeding, and meticulous data on RTI episodes and hospital admissions are needed to find tools that accurately predict who may be at risk of RTI. Research examining whether cut-offs can differentiate participants who had an RTI in the past is an initial step to finding sensitive markers that predict who may be at risk of developing an RTI in the future.

This study's third finding was that a single session of LVR improved C_{rs}, particularly in participants with MND. These results are in agreement with those of Molgat-Seon *et al*, who conducted a similar study in 12 participants with slowly progressive NMD.[10] The ~10% increase in C_{rs} we observed is smaller than their ~40% improvement and may reflect our lower and broader range of values (figure 4). Other studies measuring the effect of assisted inflation on C_L found no mean improvement,[4 29] although individual responders were identified.[29] In the absence of invasive measurements, we are unable to determine the mechanism underpinning this improvement, however, the change may potentially be attributable to alveolar recruitment, transient reversal of regional ribcage stiffness and/or measurement repeatability.

LIC also improved following therapy; participants could inflate a mean additional 130mL (5–210mL) compared with baseline. We observed no change in VC and speculate that this improvement may reflect improved technique in this naïve cohort rather than recruitment of derecruited lung tissue per se. Assisted PCF_{LIC} increased after the single session with a concomitant improvement in the PCF_{LIC} minus PCF difference; the putative cough augmentation effect of LVR.

Other research using LVR, an MI-E device or mouthpiece NIV to deliver assisted inflation therapy has likewise demonstrated no[10 37] or little[9 38] effect on VC and/or unassisted PCF. In a study of nine participants with DMD, MI-E produced a statistically significant increase in VC immediately post-therapy that dissipated by 1 hour,[38] however, the mean improvement of 8% is within the error of this measurement[13] and may not be clinically important. Cleary *et al* reported that LVR had a positive effect on VC, however, this can largely be attributable to higher values between-arms at 15 min post-therapy in this cross-over study rather than a within-group time effect, with the mean increase pre–post LVR of 70mL (~3% of baseline) not statistically different.[9] The current cohort of 78 adults is larger than all previous studies combined and suggests that a single assisted inflation session is

unlikely to improve VC in a stable population; whether there is benefit when patients are acutely unwell with an RTI was not studied.

With regard to static lung volumes, we obtained pre–post measurements in 49 participants. We suspect the statistically significant decrease in FRC and TLC we found on linear model analyses reflects test–retest variability and/or participant fatigue rather than a clinically important finding, as it was not significant on post hoc comparison (eg, FRC observed mean decrease of 30mL (–100, +30mL), p=0.348). These data add to previous small samples that reported no change in static lung volumes following a session of assisted inflation therapy.[4 10]

Study limitations

This observational study has demonstrated associations between markers of respiratory function, and between respiratory function and self-reported RTI. These associations should not be interpreted as causation, but do add to our understanding of respiratory dysfunction in adults with NMD and highlight the need for prospective longitudinal data.

The pulse inflation C_{rs} method was chosen to optimise participation in this study population. Oesophageal balloon catheter insertion would have enabled partitioning of C_L and C_{CW}, however, this was not clinically or experimentally feasible. Using this non-invasive technique and stringent methodology we obtained reproducible values in 90% of this severely impaired sample.

The retrospective, self-report of RTI may have resulted in measurement error and/or (recall) bias. We used a broad RTI definition and contacted healthcare providers if participants were uncertain.

We did not measure bulbar function in all participants and used the ALSFRS-R bulbar subscore in participants with MND. More thorough assessment of bulbar function and secretion load is needed to evaluate cough effectiveness, airway protection, airway clearance and to help determine factors contributing to RTI.

The pre–post intervention study assessed the physiological effect of LVR immediately post therapy. The comprehensive nature and time required to complete these assessments precluded multiple repeated measures, and as such we are unable to comment on the duration of the observed effects.

CONCLUSION

In this large study of participants with NMD and respiratory system impairment, people with long-standing and slowly progressive NMD had lower lung volumes and C_{rs} compared with those with rapidly progressive MND, but similar severity of respiratory muscle weakness. We speculate that ventilatory restriction in NMD is related to weakness initially, with chest wall and/or lung tissue stiffness potentiating lung volume loss over time. Reduced lung volume was also related to self-report of an RTI in the

previous year, however, VC and PCF thresholds were not discriminatory, indicating that participants could have poor respiratory function but no RTI history. There is a great need for prospective research comprising broad longitudinal assessments and accurate collection of clinical outcomes including hospital admissions, in order to understand factors contributing to respiratory decline and RTI, and how to prevent them.

This study also demonstrated that a single session of LVR can improve C_{rs} in participants naïve to this technique. The finding that low C_{rs} is a characteristic of respiratory dysfunction in this population, and that it is amenable to assisted inflation therapy, provides evidence of a potentially modifiable pathway for slowing lung volume decline. These data support the clinical and biological rationale for regular LVR, as recommended in clinical practice guidelines for people with NMD. An RCT of regular LVR is needed to determine whether the addition of daily therapy has a sustained effect on lung volumes, C_{rs} or participant quality of life.

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REFERENCES

1. Berlowitz DJ, Howard ME, Fiore JF, *et al*. Identifying who will benefit from non-invasive ventilation in amyotrophic lateral sclerosis/motor neurone disease in a clinical cohort. *J Neurol Neurosurg Psychiatry* 2016;87:280–6.
2. Gozal D. Pulmonary manifestations of neuromuscular disease with special reference to Duchenne muscular dystrophy and spinal muscular atrophy. *Pediatr Pulmonol* 2000;29:141–50.
3. De Troyer A, Borenstein S, Cordier R. Analysis of lung volume restriction in patients with respiratory muscle weakness. *Thorax* 1980;35:603–10.
4. De Troyer A, Deisser P. The effects of intermittent positive pressure breathing on patients with respiratory muscle weakness. *Am Rev Respir Dis* 1981;124:132–7.
5. Estenne M, Heilporn A, Delhez L, *et al*. Chest wall stiffness in patients with chronic respiratory muscle weakness. *Am Rev Respir Dis* 1983;128:1002–7.
6. Chatwin M, Toussaint M, Gonçalves MR, *et al*. Airway clearance techniques in neuromuscular disorders: a state of the art review. *Respir Med* 2018;136:98–110.
7. Birnkrant DJ, Bushby K, Bann CM, *et al*. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol* 2018;17:347–61.
8. Finkel RS, Mercuri E, Meyer OH, *et al*. Diagnosis and management of spinal muscular atrophy: Part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord* 2018;28:197–207.
9. Cleary S, Misiaszek JE, Kalra S, *et al*. The effects of lung volume recruitment on coughing and pulmonary function in patients with ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14:111–5.
10. Molgat-Seon Y, Hannan LM, Dominelli PB, *et al*. Lung volume recruitment acutely increases respiratory system compliance in individuals with severe respiratory muscle weakness. *ERJ Open Res* 2017;3:00135-2016–2016.
11. Quanjer PH, Stanojevic S, Cole TJ, *et al*. Multi-Ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
12. Cedarbaum JM, Stambler N, Malta E, *et al*. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (phase III). *J Neurol Sci* 1999;169:13–21.
13. Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
14. Robinson PD, Latzin P, Verbanck S, *et al*. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. *Eur Respir J* 2013;41:507–22.
15. American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002;166:518–624.
16. Kelley A, Garshick E, Gross ER, *et al*. Spirometry testing standards in spinal cord injury. *Chest* 2003;123:725–30.
17. Suratt PM, Owens DH, Kilgore WT, *et al*. A pulse method of measuring respiratory system compliance. *J Appl Physiol Respir Environ Exerc Physiol* 1980;49:1116–21.

18 Bruschi C, Cerveri I, Zoia MC, *et al*. Reference values of maximal respiratory mouth pressures: a population-based study. *Am Rev Respir Dis* 1992;146:790–3.

19 Uldry C, Fitting JW. Maximal values of sniff nasal inspiratory pressure in healthy subjects. *Thorax* 1995;50:371–5.

20 Miller RG, Jackson CE, Kasarskis EJ, *et al*. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009;73:1218–26.

21 Bott J, Blumenthal S, Buxton M, *et al*. Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. *Thorax* 2009;64 Suppl 1:i1–52.

22 Hull J, Aniapravan R, Chan E, *et al*. British thoracic Society guideline for respiratory management of children with neuromuscular weakness. *Thorax* 2012;67 Suppl 1:i1–40.

23 Bach JR, Ishikawa Y, Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. *Chest* 1997;112:1024–8.

24 Dohna-Schwake C, Ragette R, Teschler H, *et al*. Predictors of severe chest infections in pediatric neuromuscular disorders. *Neuromuscul Disord* 2006;16:325–8.

25 Estenne M, Gevenois PA, Kinnear W, *et al*. Lung volume restriction in patients with chronic respiratory muscle weakness: the role of microatelectasis. *Thorax* 1993;48:698–701.

26 Hart N, Cramer D, Ward SP, *et al*. Effect of pattern and severity of respiratory muscle weakness on carbon monoxide gas transfer and lung volumes. *Eur Respir J* 2002;20:996–1002.

27 Trebbia G, Lacombe M, Fermanian C, *et al*. Cough determinants in patients with neuromuscular disease. *Respir Physiol Neurobiol* 2005;146:291–300.

28 Gibson GJ, Pride NB, Davis JN, *et al*. Pulmonary mechanics in patients with respiratory muscle weakness. *Am Rev Respir Dis* 1977;115:389–95.

29 Lechtzin N, Shade D, Clawson L, *et al*. Supramaximal inflation improves lung compliance in subjects with amyotrophic lateral sclerosis. *Chest* 2006;129:1322–9.

30 Vitacca M, Clini E, Facchetti D, *et al*. Breathing pattern and respiratory mechanics in patients with amyotrophic lateral sclerosis. *Eur Respir J* 1997;10:1614–21.

31 LoMauro A, Romei M, D'Angelo MG, *et al*. Determinants of cough efficiency in Duchenne muscular dystrophy. *Pediatr Pulmonol* 2014;49:357–65.

32 Vender RL, Mauger D, Walsh S, *et al*. Respiratory systems abnormalities and clinical milestones for patients with amyotrophic lateral sclerosis with emphasis upon survival. *Amyotroph Lateral Scler* 2007;8:36–41.

33 Lechtzin N, Wiener CM, Clawson L, *et al*. Hospitalization in amyotrophic lateral sclerosis: causes, costs, and outcomes. *Neurology* 2001;56:753–7.

34 Sancho J, Servera E, Díaz J, *et al*. Predictors of ineffective cough during a chest infection in patients with stable amyotrophic lateral sclerosis. *Am J Respir Crit Care Med* 2007;175:1266–71.

35 Rose L, McKim D, Leasa D, *et al*. Patterns of healthcare utilisation for respiratory complications of adults with neuromuscular disease: a population study. *Eur Respir J* 2018;52:1800754.

36 Sancho J, Servera E, Bañuls P, *et al*. Predictors of need for noninvasive ventilation during respiratory tract infections in medically stable, non-ventilated subjects with amyotrophic lateral sclerosis. *Respir Care* 2015;60:492–7.

37 Cesareo A, LoMauro A, Santi M, *et al*. Acute effects of mechanical insufflation-exsufflation on the breathing pattern in stable subjects with Duchenne muscular dystrophy. *Respir Care* 2018;63:955–65.

38 Meric H, Falaize L, Pradon D, *et al*. Short-Term effect of volume recruitment-derecruitment manoeuvre on chest-wall motion in Duchenne muscular dystrophy. *Chron Respir Dis* 2017;14:110–6.

39 Smith RA, Macklin EA, Myers KJ, *et al*. Assessment of bulbar function in amyotrophic lateral sclerosis: validation of a self-report scale (center for neurologic study bulbar function scale). *Eur J Neurol* 2018;25:907–66.

40 Bach JR, Saporito LR. Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure. A different approach to weaning. *Chest* 1996;110:1566–71.