Title - The Impact of Lung Volume Recruitment on Pulmonary Function in Progressive Childhood Onset Neuromuscular Disease: A Systematic Review

Abstract

Objectives The focus of this systematic review was to consider whether Lung Volume Recruitment (LVR) has an impact on pulmonary function test parameters in individuals with progressive childhood onset neuromuscular diseases. The review was registered on PROSPERO (# CRD42019119541). **Data Sources** A systematic search of CINAHL, MEDLINE, AMED, EMCARE, Scopus and Open Grey databases was undertaken in January 2019 considering LVR in the respiratory management of childhood onset neuromuscular diseases. **Study selection** Studies were included if either manual resuscitator bags, or volume-controlled ventilators, were used to perform LVR with participants over 6 years of age. Critical appraisal tools from the Joanna Briggs Institute were utilised to assess the quality of studies. Nine studies were identified with six of sufficient quality to be included in the review. **Data Extraction** Data extraction utilised a tool adapted from the Cochrane effective practice and organisation of care group. **Data Synthesis** Results were compiled using a narrative synthesis approach focused on peak cough flow, forced vital capacity and maximum inspiratory capacity outcomes. **Conclusions** Limited evidence suggests an immediate positive effect of LVR on peak cough flow and a potential long-term impact on the rate of forced vital capacity decline. Considering the accepted correlation between forced vital capacity and morbidity this review suggests LVR be considered for individuals with childhood onset neuromuscular diseases once forced vital capacity starts to deteriorate. This review is limited by small sample sizes and overall paucity of evidence considering LVR in this population group. Controlled trials with larger sample sizes are urgently needed.

Keywords :- Neuromuscular disorder, Spinal muscular atrophy, Dystrophy, Lung Volume Recruitment, Breath Stacking, Air stacking

Abbreviations

LVR – Lung Volume Recruitment

NMD - neuromuscular diseases

EBM - Evidence based medicine

RCT – Randomised controlled trial

MND - Motor Neuron disease

DMD - Duchenne Muscular dystrophy

CMD - congenital muscular dystrophies

SMA - Spinal Muscular atrophy

PCF – Peak Cough Flow

VC – Vital Capacity

MIC – Maximal inspiratory capacity

IPPB - Intermittent Positive Pressure Breathing

NIV Non-Invasive Ventilation

GPB - Glossopharyngeal breathing

MI-E - Manual Insufflator-Exsufflator

FVC – Forced vital capacity

MIP – Maximal inspiratory pressure

MEP – Maximal expiratory pressure

ATS – American thoracic society

CASP – Critical Appraisal Skills Programme

SURE - Specialist Unit for Review Evidence

JBI - Joanna Briggs Institute

MS – Multiple sclerosis

ANCOVA – Analysis of Co-variance

The advent of Non-invasive ventilation (NIV), supporting tidal volume breathing has been pivotal in increasing the life expectancy of many of those with Neuromuscular Diseases (NMD) [1]. Despite this, recognition is growing that ventilation alone is insufficient to manage the vicious cycle of increasing load and progressive respiratory muscle weakness that these diseases present [2].

In NMDs muscle weakness renders the spontaneous sigh breaths, yawns, and coughs present in unaffected individuals, ineffective. Proposed to maintain lung expansion, compliance, and secretion clearance [3], the absence of these supra-tidal inhalations leaves individuals at risk of deteriorating thoracic cage mobility, reduced pulmonary compliance and elevated risk of respiratory tract infections [4]. This is especially evident in childhood onset NMD's, where progressive muscle weakness occurs in the context of both pulmonary and musculoskeletal growth. The resulting scoliosis, chest wall deformities and potentially diminished lung growth, serves only to further increase the work of breathing [4].

Lung Volume Recruitment (LVR) is a simple inexpensive technique used to augment inspiration [5], either prior to a cough or on a regular basis to mimic lost spontaneous deep breathing activities. [6]. LVR has demonstrated effectiveness in improving assisted Peak Cough Flow (PCF) values across the spectrum of adult onset NMD's [7, 8]. The role of the technique in progressive childhood onset NMD's, has, however, yet to be clearly defined. Furthermore, the long-term impact of LVR on unassisted PCF, Forced Vital Capacity (FVC) and Maximum Inspiratory Capacity (MIC) remains unclear. Searches of the Cochrane Library, Joanna Briggs Institute (JBI) and Prospero did not identify any existing systematic reviews or protocols.

This systematic review aims to answer the review question: - Does LVR have an impact on pulmonary function test parameters in individuals with progressive childhood onset NMD's?

2.0 Materials and participants

Studies were considered for inclusion in this systematic review if study participants were over six years of age with a formal diagnosis of progressive childhood onset NMD. Though LVR as a technique is proposed to be easily mastered, even within paediatrics [3], reliable and consistent performance of pulmonary function tests is not felt to be achieved until 5-6 years of age [9]. No upper age limit was considered necessary. Studies were also required to undertake: -

- LVR using a volume-controlled ventilator or manual resuscitator bag [10].
- Comparison of LVR to baseline function or no treatment
- Peak Cough Flow (PCF), Forced Vital Capacity (FVC) or Maximal inspiratory capacity (MIC) as outcomes of interest.
- The study according to any experimental study design.

Studies were excluded if they considered:-

• Mixed populations of NMD's i.e. combination of childhood onset and adult onset NMD's.

• LVR utilising any other strategies including Manual Insufflation-Exsufflation, Glossopharyngeal Breathing or Intermittent positive pressure breathing (IPPB)

• None of the above outcome measures

• Paediatric participants less than 6 years of age

• Case series and case study designs

• Publication not in the English language

• Acutely unwell participants.

Studies assessed as at significantly high risk of bias were also excluded from the review

2.1 Methods

Analysis methods and inclusion criteria were specified prospectively in a protocol registered on PROSPERO (International Prospective Register of Systematic Reviews) with identifier CRD42019119541. The main outcome of interest was LVR assisted PCF, with secondary outcomes focused on FVC and MIC.

2.2 Search Strategy

A systematic search of EBSCO, SCOPUS, AMED, MEDLINE, EMCARE, and Open Grey databases was undertaken from 21st-24th January 2019. The keywords utilised are identified in the supplementary material. Terms were kept intentionally broad to capture all relevant sources and support from an information specialist, was utilised. The search strategy was pilot tested, including minor diagnoses, though no additional studies were identified. No restriction regarding terms in the title or abstract was imposed. Inclusion of the comparator element, outcomes or a date limit were deemed unnecessary given the niche topic area. No limits were applied in the databases, though screening was used to include only studies in English Language (or with English language translations available) due to limitations in translation resources. One potential study was excluded due to language [11] though without translation it is unclear whether it would have fitted inclusion criteria. Database searching was completed in duplicate and supplemented by contact with study authors. In addition, forward and backward citation chaining from included studies, and review articles was undertaken with continued monitoring through database auto-alerts undertaken until September 2019. No further studies were identified. Grey literature was also included to optimise the literature search and limit the potential effects of selective publication [12].

Following the search, all identified citations were collated and uploaded into EndNote and duplicates removed. Titles and abstracts were screened against the inclusion criteria with studies fulfilling inclusion criteria, retrieved in full. Full text studies were then assessed in detail against the inclusion criteria. Those full text studies that did not meet the inclusion criteria were excluded (see supplementary material).

2.3 Quality appraisal and Data extraction

Two reviewers with postgraduate research training, critically appraised studies independently using the JBI critical appraisal tools. (see supplementary material). Discrepancies were resolved through discussion, and with a third experienced reviewer, when applicable. Studies identified as being at high risk of bias were excluded from the review.

Data was extracted utilising a tool adapted from the Cochrane Effective Practice and Organisation of Care (EPOC) group [13] (See Supplementary Material), which was cross-checked by a second reviewer for accuracy. Where clarification of elements was necessary, authors were contacted by e-mail. The primary outcome of interest was LVR assisted PCF with mean assisted PCF the principal summary measure. Secondary outcome measures focused on Maximal inspiratory capacity (MIC) and Forced vital capacity (FVC). Maximal inspiratory pressure (MIP) and Maximal expiratory pressure (MEP) were also proposed as secondary outcome measures. They were, however, removed following data extraction as only one of the included studies presented this information. Demographic information focused on the setting, mean age of participants and diagnoses, as well as baseline PCF. Variables regarding the conduct of the LVR, including dosage and equipment were also extracted.

<u>3.0 Results</u>

Of the nine studies identified (Figure 1), critical appraisal suggested three studies were at high risk of bias due to limited sample information, absence of detail regarding confounding variables and lack of standardisation in outcome measurement. As a result, these were excluded from the review prior to data extraction. Full details are outlined in supplementary material.

Though outcome data from all studies is broadly homogenous, heterogeneity within study methodology, coupled with the position of all studies at level 3 or 4 on the hierarchy of evidence [14] precluded quality meta-analysis [15]. As a result, a text-based, narrative synthesis approach was undertaken using an established framework [16].

3.1 Preliminary Synthesis

Preliminary synthesis of the six identified studies indicated wide variation in the setting, duration, methodology and baseline function of participants, though mean age, diagnosis implementation methods and equipment were relatively consistent (Table 1).

Table 1 – Baseline characteristics and methodology

Article	Setting	Sample size	Mean Age (years) (range)	Diagnoses	Baseline PCF (L/min) (mean)	Equipment	Delivered by	Method and dosage	Duration (Years)
Katz et al. [18]	OP rehab Ontario Canada	16	19.3 (Median) (8.6-33)	DMD.	90 (Median)	Resuscitator bag with one-way valve	Respiratory therapist Care giver Long-term	3-5 consecutive insufflations 3-5 cycles twice daily	6.1 (1.7-16.1)
McKim et al. [19]	OP rehab Ontario, Canada	22	19.6 (17.6-24.6)	DMD.	144.8	Resuscitator bag with one-way valve	Respiratory therapist, Care giver Long-term.	3-5 consecutive insufflations 3-5 cycles twice daily	3.75 (Median) No range provided
Marques et al. [20]	NMD OP, Sao Paulo, Brazil	18	15.4 (7-23)	10 CMD, 4 SMA II, 4 SMA III	258	Resuscitator bag exhale port blocked	Respiratory therapist, Care giver Long-term.	10 cycles Split over 3 sessions/day	Not stated (4-6 months)
Brito et al. [5]	Paeds NIV OP Sao Paulo, Brazil	28	20.0 (>10 years Range not stated)	DMD.	171 Litres/min)	Resuscitator bag with one-way valve	Respiratory therapist	3 consecutive insufflations	N/A
Ishikawa et al. [17]	Long-term care facility Japan	61	22.1 (12-36)	DMD.	138 Litres/min)	Resuscitator bag or volume set ventilator.	Respiratory therapist	Consecutive insufflations of 1 litre	N/A
Toussaint et al. [10]	NMD OP rehab, Brussels Belgium	52 (27 Ventilator Group) (25 resuscitator bag group)	25.3 (> 18 years) 24.7 (>18years)	DMD	132 Litres/min) 125 Litres/min)	Resuscitator bag or volume set ventilator.	Experienced physiotherapist	2-3 consecutive insufflations,	N/A

3.2 Immediate Effects of LVR

All the studies provide data demonstrating the immediate impact of LVR on PCF (Table 2). In Brito et. al.[5], Ishikawa et al.[17], and Toussaint et al.[10], LVR was demonstrated to have a statistically significant impact on PCF. In Katz et al.[18], McKim et al.[19] and Marques et al.[20], descriptive statistics are presented, from which percentage increase in PCF can be calculated. Marked homogeneity is evident with immediate increases in PCF values with use of LVR evident across all studies.

Table 2 – Immediate and long-term effects of Lung Volume Recruitment on LVR assisted (aPCF) and Unassisted (uPCF) Peak Cough Flow.

Study		Mean uPCF pre regular LVR[1] (Litres/min)	Mean uPCF post regular LVR[2] (Litres/min)	P value	Mean aPCF pre-regular LVR[3] (Litres/min)	Mean aPCF post-regular LVR [4] (Litres/min)	P value (% increase)
Ishikawa et al.[17]		138 (+/- 70)	-	-	236 (+/- 68)	-	0.0001 (71%)
Brito et al.[5]		171 (+/- 67)	-	-	231 (+/- 81)	-	0.001 (35%)
Toussaint et al.[10]	Ventilator group	132 (+/- 55)	-	-	199	-	0.001 (51%)
	Resus bag group	125 (+/-52)			186		0.001 (49%)
Marques et al. 2014		257.8 (+/- 84.3)	277.9 (+/- 90.2)	<0.0001	272.7 (+/- 82.9)	299.8 (+/- 98.2)	<0.0001
Katz et al. 2015 (Median/IQR)		90 (60-115)	90 (70-108)	Not assessed	200 (145-243)	205 (140-240)	Not assessed
McKim et al. 2012		144.8 (+/-106.9)	128.3 (+/- 80.1)	0.235	232.8 (+/- 103.3)	216.1 (+/- 91.0)	0.514

[1] Mean Unassisted PCF readings without regular LVR prior

[2] Mean Unassisted PCF readings with regular LVR prior

[3] Mean LVR assisted PCF readings without regular LVR prior

[4] Mean LVR assisted PCF readings with regular LVR prior

3.3 Long-term Effects of LVR

Beyond the immediate effects of LVR on PCF, three of the studies [18-20] also considered the longer-term implications of daily LVR use on respiratory function parameters (Table 2).

Initial inspection of outcome data between studies considering the longitudinal effects of LVR on PCF appear inconsistent. Following a daily LVR programme, Marques et al.[20] reported a significant difference in both PCF readings taken without LVR assistance (unassisted PCF) and PCF readings assisted by LVR (assisted PCF)(Table 2). In contrast both McKim et al.[19] and Katz et al.[18] found no significant differences, following a daily LVR programme, in either LVR assisted or unassisted PCF values.

FVC data from the three long term studies demonstrated a similar pattern to PCF trends (Table 3). A small increase in FVC was evident in Marques et al's [20] entire cohort over the study duration. Rather than focus on absolute FVC values both McKim et al.[19] and Katz et al.[18] considered the rate of decline in percent predicted values. Prior to LVR initiation, Katz et al.[18] and McKim et al.[19] reported an FVC decline of 4.5% and 4.7 % predicted per year respectively. Following LVR this reduced to 0.5% predicted per year in both studies. McKim et al.[19] statistically analysed the mean change between the two rates, noting a statistically significant 89% improvement in the rate of FVC decline post LVR initiation ($p<0.000$).

MIC is less well considered with none of the three longitudinal studies statistically analysing changes over the studies duration. Marques et al.[20] identifies a very small increase in MIC over the studies duration where McKim et al.[19] identifies somewhat greater MIC values over time (Table 3). Katz et al.[18] only documents change in the percent predicted MIC values. Beyond absolute values, Katz et al.[18] also considers the difference in passive and active inspiratory capacity over time through comparison of the difference in MIC and FVC. An increased difference is noted between these two values of 0.02Litres/year for up to 10 years of follow-up (p=0.06).

Table 3 - Long-term impact of LVR on Forced Vital Capacity and Maximum inspiratory capacity

Study		Mean FVC pre regular LVR (Litres) (SD)	Mean FVC (Litres) post regular LVR (SD)	Mean MIC (Litres) (SD) pre- regular LVR	Mean MIC (SD) (Litres) post-regular LVR	Duration (years) (range)
Marques et al. [20]	Combined	1.78 (+/- 0.60)	1.83 (+/- 0.63)	2.046 (+/-0.634)	2.057 (+/- 0.673)	0.3-0.5 (4-6 months)
	With scoliosis	1.469 (+/- 0.646)	1.467 (+/- 0.672)			
	Without scoliosis	2.10 (+/- 0.332)	2.19 (+/- 0.315)			
Katz et al.[18]		0.5 (0.4-0.7) Median (IQR) 13.5%predicted (8-20.3 %)	0.6 (0.4-0.7) Median (IQR) 13.0% predicted (8.8-17.3)	1.3 L (0.8-4.0) Median (IQR)	1.6L (1.2-1.8) Median (IQR)	6.1 (median) (1.7-16.1 years)
McKim et al.[19]		1.0 (+/- 0.7) 21.8 % predicted (+/- 16.9)	21.7% predicted (+/- 15.4)	1.6 (+/-0.9) 35.8 % predicted (+/- 18.1)	38.2% predicted	3.75 (Median) No range provided

4.0 Discussion

4.1 Short-term impact of LVR

All six studies demonstrated a consistently positive impact of LVR on PCF's, with PCF values increasing by 6-122%. This is supported throughout the wider literature in NMD's with increases 53%. [21] 65% [22]and 69%[23] reported. Similar results were also observed in the three excluded studies considered for this review [1,24,25]. Although all these studies may be considered reasonably low on the hierarchy of evidence (Levels 3 or 4), lack control groups and are arguably at high risk of selection and performance biases, the corroboration of results between all studies suggests LVR may be considered an effective, immediate means of increasing PCF.

On closer examination the magnitude of increase in PCF is markedly lower in Marques et al.[20] than the other five studies. Sub-group analysis at baseline showed no statistical differences in the response to LVR between Spinal Muscular Atrophy (SMA) and Congenital Muscular Dystrophy (CMD) diagnoses. Despite this Marques et al's [20] cohort does present with the lowest mean age (15.4 years), lowest incidence of reported scoliosis and highest baseline PCF and FVC (257.8Litres/min and 1.78 Litres). Given measurement differences between spirometers and peak flow meters, care needs to be taken in comparing absolute PCF values between studies, but FVC readings suggest better overall respiratory function at baseline in Marques et al's [20] cohort than those in the other studies (Table 3).

This concept of baseline function as a moderator is further developed through a sub-group analysis undertaken by Ishikawa et al. [17]. They analysed participants in quartiles based on their baseline PCF, concluding that for participants in the three lowest quartiles (baseline PCF of <190Litres/min), the impact of LVR was statistically significant (P<0.007). However, in the strongest quartile (baseline PCF >190Litres/min and mean baseline PCF 231.8L/min) the difference between baseline PCF and PCF augmented by LVR, was not statistically significant ($p>0.05$).

Ishikawa et al's [17] theory that the immediate effects of LVR may be greatest in those with lower baseline function is supported by Toussaint et al.[10]. Similar conclusions have been drawn in other studies both in adult [26] and paediatric populations [3]. Toussaint et al [10] also suggests a 'floor effect' may exist. Sub-group analysis amongst their cohort demonstrated participants with a PCF of under 90Litres/min were unable to augment their PCF sufficiently with LVR alone to exceed the widely accepted minimum effective PCF of 160Litres/min [27]. They conclude that individuals with very low baseline PCF will benefit from combining LVR with manually assisted cough or using Manual Insufflator-Exsufflator to achieve effective PCF.

Beyond baseline function, the presence of scoliosis [20] is also proposed as a potential variable impacting the effectiveness of LVR. Scoliosis is widely acknowledged to reduce respiratory system compliance and impact on lung function [28]. Despite this no clear evidence exists in the studies analysed, nor in the wider literature, to suggest the presence of scoliosis impacts the effectiveness of LVR [29,30]. LVR may not be equally beneficial for all individuals with progressive childhood onset NMD's [16, 17]. Further evidence regarding the characteristics of those who respond positively to LVR versus 'non-responders', is, however, currently lacking [31].

Evidence from both this review and the wider literature suggests that, clinically, resources should be prioritised to ensure individuals with lower PCF values have access to LVR. This would ensure treatment effects are maximised and minimum effective cough flows of around 160Litres/minute [31] are achieved. Defining the point at which LVR initiation should be considered clinically is, however, challenging. The ATS recommends that cough augmentation strategies should be implemented once PCF values fall below 270 Litres/min [32]. The small positive effects on PCF seen in both Marques et al's [20] (baseline PCF 257.8 Litres/min) and Ishikawa et al's [17] (baseline PCF 231.8 Litres/min) results would appear to support this recommendation. The presence of scoliosis, however, should not prevent consideration of LVR as a treatment option.

4.2 Long-term impact of LVR

Though the immediate benefit of LVR on PCF is reasonably clear and consistent throughout the literature, longitudinal effects are less well defined. This is due largely to a lack of longitudinal studies and a wide variation in methodologies.

In this review, Marques et al's [20] relatively short-term study (4-6 months), was alone in demonstrating a statistically significant increase in both LVR assisted and unassisted PCF's over time (<0.0001). Katz et al.[18] reported a small increase in assisted PCF over the study duration (median 6.1 years) with regular LVR use, while McKim et al.[19] reported a decline over the median 3.75 years of LVR use. Neither of these observed interactions were significant.

The key to this apparent incongruity in outcomes may lie in the duration of the three studies, though little clarification is evident in the wider literature. Where disease progression is likely to have had limited impact on the results described in Marques et al. [20] study the extended duration of both Katz et al [18] and McKim et al [19] studies, may provide time for the progressive nature of the NMD's studied to have influenced the results.

As such the study duration may be considered a mediator variable across these longitudinal studies as the impact of LVR is countered by the progressive nature of the disorders.

Both Kang and Bach [33] and Srour et al.[7] reported longitudinal PCF changes in the sub-group defined as ‘responders’. Responders in both studies were considered those for whom LVR demonstrated an immediate improvement in PCF. Kang and Bach [33] noted that assisted PCF improved over time, while Srour et al.[7] reported a statistically significant reduction in rate of unassisted PCF decline (p = 0.042) between ‘responders’ and ‘non-responders’ to LVR. Though Kang and Bach [30] failed to explore any causative factors that resulted in participants being non-responders, Srour et al. [7] considered numerous factors including presence of scoliosis and disease modifying medications. Despite this, they concluded the only consistent association with LVR effectiveness was lower baseline function.

In the absence of clear data regarding normal PCF variability over time, the clinical relevance of the results from these small numbers of studies, is unclear [31]. Furthermore, the combination of paediatric and adult patients considered in this review’s studies is likely to further confound the results. The interplay of musculoskeletal and pulmonary growth in paediatrics, increasing PCF [34] alongside NMD progression, causing it to decline, makes it difficult to draw conclusions regarding the longitudinal impact of LVR on unassisted or assisted PCF. As a result, no definitive clinical recommendations can be made regarding the effectiveness of LVR in improving unassisted or LVR assisted PCF over time.

In contrast to PCF, FVC has a relatively, well documented longitudinal course, both in healthy individuals and those with DMD [34]. Given FVC is a variable directly related to mortality [15] any positive impact on its longitudinal progression is clinically advantageous.

Marques et al.[16] reported a 2.8% increase in absolute FVC values over the 4-6 month study duration. While Mckim et al.[15] and Katz et al.[14] both outline a 0.5% predicted annual decline in FVC following LVR initiation, compared to 4.5% and 4.8% predicted decline respectively, prior to treatment.

Results from Srour et al. [7] and Chiou et al.[35] further support these findings. Srour et al.[7] reported a statistically significant slower rate of decline in FVC amongst participants with MS who undertook regular LVR, when compared to non-responders who did not perform LVR.

The challenge in considering the rate of decline is that FVC does not deteriorate in a linear fashion. Gradual increases are seen over childhood, reaching a maximum plateau at around age 20 in healthy individuals and around age 11-14 years in DMD [35]. Following this, FVC decline in DMD is exponential, with the maximum rate of decrease around age 14-16 years [36] before asymptomatically levelling off [37].

Given both Katz et al.[18] and Marques et al.[20] considered a broad age range (8.6-33 and 7-23 years respectively), inclusion of individuals for whom absolute values of FVC were spontaneously still increasing, or stable, is highly likely. This inclusion of individuals yet to reach their maximum plateau of FVC has the potential to be a significant confounding variable in these studies. Despite this McKim et al.[19] had a much narrower aged cohort (17.6-24.6 years) but very similar rate of decline in FVC (4.5% predicted) to that reported by Katz et al.[18](4.8% predicted).

Given the use of NIV in all the longitudinal studies, prior to and following LVR initiation, for most participants, its use is unlikely to pose a significant confounding factor. The impact of steroid use is also considered negligible given only four participants in one of the studies

[19] utilised steroids, both prior to and following LVR initiation. Research findings regarding the impact of steroid use on lung function in this population group remain conflicting [38], though a positive impact on FVC and other LFT parameters was observed in DMD boys aged 10-15years [39]. As a result, evidence from this review suggests LVR may slow the decline in FVC over time, though the exact mechanism by which this may occur remains unclear. Further studies, considering LVR's effectiveness in the context of accepted FVC progression in NMD, is imperative.

A proposed mechanism for the effectiveness of LVR in slowing FVC decline is through improved respiratory system compliance secondary to regular achievement of MIC. Review findings demonstrate widely variable increases (0.5-23%) in MIC following regular LVR in the three longitudinal studies [18,19,20], none of which analysed the increases in MIC for statistical significance.

Marques et al.[20] only identify a very small increase in MIC over the studies timeline (Table 3). This may relate to the relatively short study duration, the cohort's stronger baseline function or the achievement of true MIC with LVR. Four of the studies utilise clinical assessment to ensure LVR achieves the individual's MIC. The two remaining studies [5, 20] report a standard programme of LVR. As such, it is possible that participants in both these studies were not achieving their full MIC with LVR and as such changes in capacity may be sub-optimal.

Katz et al.[18] also analysed the MIC- FVC difference noting an increase over the studies duration ($p=0.06$). Though not statistically significant, this finding illustrates that even as active capability (FVC) declines, passive capacity (MIC) can gradually increase.

Statistically significant increases in MIC with regular LVR use have, however, been demonstrated both in a cohort of mixed NMD diagnoses [26] and those with DMD [35]. Both authors propose that regular LVR increases lung expansion, limits atelectasis, and subsequently maintains passive respiratory volume, measured by MIC.

Though there is face validity to this theory, the potential role for both practice effects and improved bulbar musculature control on improving MIC readings, must also be considered [40].

Despite this, daily use of cough augmentation techniques including LVR are widely supported in numerous consensus statements on the management of SMA [41], DMD [32] and children with neuromuscular weakness [42]. This may be due, in part, to the proposed longitudinal benefits of LVR on FVC and MIC, as well as the impact on PCF.

4.3 Study Limitations

The small number and reasonably low-quality of studies available for inclusion limit this review. Furthermore, despite working with information specialists to tailor the search strategy, included studies focused predominantly on DMD, with only a single study considering SMA and CMD. This does, however, represent the largest diagnostic groups with respiratory involvement in progressive childhood onset NMDs and the current evidence base available.

It should be noted that both Katz et al.[18] and McKim et al.[19] investigated cohorts originating from the same Canadian centre during similar time periods (1992-2008 and 1991- 2008 respectively). McKim et al.[19] focused on an adult only cohort (17.6- 24.6 years old) and the impact of LVR initiation on the rate of FVC decline. Katz et al.[18] presented a broader age range (8.6-33 years) and focused on the interventions impact on MIC and VC. Due to these differences the decision was made to consider and appraise the studies individually, though an awareness of the potential for some overlap in the cohorts is acknowledged. Resource constraints regarding translation facilities may also be considered a limitation to this review as only English language studies could be included.

5.0 Conclusions

All six studies considered the immediate effect of LVR in augmenting PCF with positive effects noted in all included studies. The magnitude of the improvement in PCF appeared greatest in those with lower baseline PCF (less than 190Litres/min), though positive effects are still noted in individuals with PCF of over 250Litres/minute. Longitudinal effects of LVR on PCF are, however, far less clear with no clinical conclusion able to be drawn from the evidence available in this review. Clinically LVR should be prescribed to optimise secretion clearance, with the ATS recommendation of implementing such techniques around a baseline PCF of 270Litres/min appearing appropriate. Daily use of LVR may impact positively on PCF's over time, though further longitudinal research, utilising control groups is required.

Three of the studies considered the longitudinal effects of LVR on FVC and MIC. Though variation existed in the findings they were suggestive of an improvement in the rate of decline of FVC following LVR initiation. Considering the accepted correlation between FVC and morbidity this review suggests that LVR be considered for individuals once FVC starts to decline.

MIC did show small improvements over the studies included in this review. However, in the absence of clear data regarding MIC variability over time in progressive childhood onset NMD's, the significance of this finding is unclear.

Overall, this review suggests that LVR may have a positive impact on pulmonary function test parameters amongst individuals with progressive childhood onset NMD, though significant further research is necessary. Clinical trials with larger sample sizes and control groups are urgently needed to determine the true effectiveness of LVR as an intervention.

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Figures

Figure 1 - Prisma Flow diagram