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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

	GPB - Glossopharyngeal breathing
LVR – Lung Volume Recruitment	MI-E - Manual Insufflator-Exsufflator
NMD - neuromuscular diseases	FVC – Forced vital capacity
EBM - Evidence based medicine	MIP – Maximal inspiratory pressure
RCT – Randomised controlled trial	
MND - Motor Neuron disease	MEP – Maximal expiratory pressure
DMD - Duchenne Muscular dystrophy	ATS – American thoracic society
CMD - congenital muscular dystrophies	CASP – Critical Appraisal Skills Programme
SMA - Spinal Muscular atrophy	SURE - Specialist Unit for Review Evidence
PCF – Peak Cough Flow	JBI - Joanna Briggs Institute
VC – Vital Capacity	MS – Multiple sclerosis
MIC – Maximal inspiratory capacity	ANCOVA – Analysis of Co-variance
IPPB - Intermittent Positive Pressure Breathing	
NIV Non-Invasive Ventilation	

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

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

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

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

25

26 **2.0 Materials and participants**

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

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

38 Studies were excluded if they considered:-

- 39 • Mixed populations of NMD's i.e. combination of childhood onset and adult onset NMD's.
- 40 • LVR utilising any other strategies including Manual Insufflation-Exsufflation,
41 Glossopharyngeal Breathing or Intermittent positive pressure breathing (IPPB)
- 42 • None of the above outcome measures
- 43 • Paediatric participants less than 6 years of age

- 44 • Case series and case study designs
- 45 • Publication not in the English language

- 46 • Acutely unwell participants.

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

48 **2.1 Methods**

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

53

54 **2.2 Search Strategy**

55 A systematic search of EBSCO, SCOPUS, AMED, MEDLINE, EMCARE, and Open Grey
56 databases was undertaken from 21st-24th January 2019. The keywords utilised are identified
57 in the supplementary material. Terms were kept intentionally broad to capture all relevant
58 sources and support from an information specialist, was utilised. The search strategy was
59 pilot tested, including minor diagnoses, though no additional studies were identified. No
60 restriction regarding terms in the title or abstract was imposed. Inclusion of the comparator
61 element, outcomes or a date limit were deemed unnecessary given the niche topic area. No
62 limits were applied in the databases, though screening was used to include only studies in English
63 Language (or with English language translations available) due to limitations in translation
64 resources. One potential study was excluded due to language [11] though without
65 translation it is unclear whether it would have fitted inclusion criteria. Database searching

66 was completed in duplicate and supplemented by contact with study authors. In addition,
67 forward and backward citation chaining from included studies, and review articles was
68 undertaken with continued monitoring through database auto-alerts undertaken until
69 September 2019. No further studies were identified. Grey literature was also included to
70 optimise the literature search and limit the potential effects of selective publication [12].

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

76 **2.3 Quality appraisal and Data extraction**

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

82 Data was extracted utilising a tool adapted from the Cochrane Effective Practice and
83 Organisation of Care (EPOC) group [13] (See Supplementary Material), which was cross-
84 checked by a second reviewer for accuracy. Where clarification of elements was necessary,
85 authors were contacted by e-mail. The primary outcome of interest was LVR assisted PCF
86 with mean assisted PCF the principal summary measure. Secondary outcome measures
87 focused on Maximal inspiratory capacity (MIC) and Forced vital capacity (FVC). Maximal
88 inspiratory pressure (MIP) and Maximal expiratory pressure (MEP) were also proposed as

89 secondary outcome measures. They were, however, removed following data extraction as
90 only one of the included studies presented this information. Demographic information
91 focused on the setting, mean age of participants and diagnoses, as well as baseline PCF.
92 Variables regarding the conduct of the LVR, including dosage and equipment were also
93 extracted.

94 **3.0 Results**

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

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

104

105 **3.1 Preliminary Synthesis**

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

109 **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

111 **3.2 Immediate Effects of LVR**

112 All the studies provide data demonstrating the immediate impact of LVR on PCF (Table 2).

113 In Brito et. al.[5], Ishikawa et al.[17], and Toussaint et al.[10], LVR was demonstrated to have

114 a statistically significant impact on PCF. In Katz et al.[18], McKim et al.[19] and Marques et

115 al.[20], descriptive statistics are presented, from which percentage increase in PCF can be

116 calculated. Marked homogeneity is evident with immediate increases in PCF values with use

117 of LVR evident across all studies.

118 **Table 2** – Immediate and long-term effects of Lung Volume Recruitment on LVR assisted

119 (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		
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

120 ¹ Mean Unassisted PCF readings without regular LVR prior

121 ² Mean Unassisted PCF readings with regular LVR prior

122 ³ Mean LVR assisted PCF readings without regular LVR prior

123 ⁴ Mean LVR assisted PCF readings with regular LVR prior

124 **3.3 Long-term Effects of LVR**

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

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

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

142

143 MIC is less well considered with none of the three longitudinal studies statistically analysing
144 changes over the studies duration. Marques et al.[20] identifies a very small increase in MIC
145 over the studies duration where McKim et al.[19] identifies somewhat greater MIC values

146 over time (Table 3). Katz et al.[18] only documents change in the percent predicted MIC
 147 values. Beyond absolute values, Katz et al.[18] also considers the difference in passive and
 148 active inspiratory capacity over time through comparison of the difference in MIC and FVC.
 149 An increased difference is noted between these two values of 0.02Litres/year for up to 10
 150 years of follow-up (p=0.06).

151 **Table 3** - Long-term impact of LVR on Forced Vital Capacity and Maximum inspiratory
 152 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

153
 154
 155
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 157

158 **4.0 Discussion**

159 **4.1 Short-term impact of LVR**

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

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

177 This concept of baseline function as a moderator is further developed through a sub-group
178 analysis undertaken by Ishikawa et al. [17]. They analysed participants in quartiles based on
179 their baseline PCF, concluding that for participants in the three lowest quartiles (baseline
180 PCF of <190Litres/min), the impact of LVR was statistically significant ($P<0.007$). However, in

181 the strongest quartile (baseline PCF >190Litres/min and mean baseline PCF 231.8L/min) the
182 difference between baseline PCF and PCF augmented by LVR, was not statistically significant
183 ($p>0.05$).

184 Ishikawa et al's [17] theory that the immediate effects of LVR may be greatest in those with
185 lower baseline function is supported by Toussaint et al.[10]. Similar conclusions have been
186 drawn in other studies both in adult [26] and paediatric populations [3]. Toussaint et al [10]
187 also suggests a 'floor effect' may exist. Sub-group analysis amongst their cohort
188 demonstrated participants with a PCF of under 90Litres/min were unable to augment their
189 PCF sufficiently with LVR alone to exceed the widely accepted minimum effective PCF of
190 160Litres/min [27]. They conclude that individuals with very low baseline PCF will benefit
191 from combining LVR with manually assisted cough or using Manual Insufflator-Exsufflator to
192 achieve effective PCF.

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

201 Evidence from both this review and the wider literature suggests that, clinically, resources
202 should be prioritised to ensure individuals with lower PCF values have access to LVR. This
203 would ensure treatment effects are maximised and minimum effective cough flows of

204 around 160Litres/minute [31] are achieved. Defining the point at which LVR initiation should
205 be considered clinically is, however, challenging. The ATS recommends that cough
206 augmentation strategies should be implemented once PCF values fall below 270 Litres/min
207 [32]. The small positive effects on PCF seen in both Marques et al's [20] (baseline PCF 257.8
208 Litres/min) and Ishikawa et al's [17] (baseline PCF 231.8 Litres/min) results would appear to
209 support this recommendation. The presence of scoliosis, however, should not prevent
210 consideration of LVR as a treatment option.

211 **4.2 Long-term impact of LVR**

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

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

221 The key to this apparent incongruity in outcomes may lie in the duration of the three
222 studies, though little clarification is evident in the wider literature. Where disease
223 progression is likely to have had limited impact on the results described in Marques et al.
224 [20] study the extended duration of both Katz et al [18] and McKim et al [19] studies, may
225 provide time for the progressive nature of the NMD's studied to have influenced the results.

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

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

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

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

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

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

257 The challenge in considering the rate of decline is that FVC does not deteriorate in a linear
258 fashion. Gradual increases are seen over childhood, reaching a maximum plateau at around
259 age 20 in healthy individuals and around age 11-14 years in DMD [35]. Following this, FVC
260 decline in DMD is exponential, with the maximum rate of decrease around age 14-16 years
261 [36] before asymptotically levelling off [37].

262 Given both Katz et al.[18] and Marques et al.[20] considered a broad age range (8.6-33 and
263 7-23 years respectively), inclusion of individuals for whom absolute values of FVC were
264 spontaneously still increasing, or stable, is highly likely. This inclusion of individuals yet to
265 reach their maximum plateau of FVC has the potential to be a significant confounding
266 variable in these studies. Despite this McKim et al.[19] had a much narrower aged cohort
267 (17.6-24.6 years) but very similar rate of decline in FVC (4.5% predicted) to that reported by
268 Katz et al.[18](4.8% predicted).

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

272 [19] utilised steroids, both prior to and following LVR initiation. Research findings regarding
273 the impact of steroid use on lung function in this population group remain conflicting [38],
274 though a positive impact on FVC and other LFT parameters was observed in DMD boys aged
275 10-15years [39]. As a result, evidence from this review suggests LVR may slow the decline in
276 FVC over time, though the exact mechanism by which this may occur remains unclear.
277 Further studies, considering LVR's effectiveness in the context of accepted FVC progression
278 in NMD, is imperative.

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

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

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

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

298 Though there is face validity to this theory, the potential role for both practice effects and
299 improved bulbar musculature control on improving MIC readings, must also be considered
300 [40].

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

305 **4.3 Study Limitations**

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

312 It should be noted that both Katz et al.[18] and McKim et al.[19] investigated cohorts
313 originating from the same Canadian centre during similar time periods (1992-2008 and
314 1991- 2008 respectively). McKim et al.[19] focused on an adult only cohort (17.6- 24.6 years
315 old) and the impact of LVR initiation on the rate of FVC decline. Katz et al.[18] presented a

316 broader age range (8.6-33 years) and focused on the interventions impact on MIC and VC.
317 Due to these differences the decision was made to consider and appraise the studies
318 individually, though an awareness of the potential for some overlap in the cohorts is
319 acknowledged. Resource constraints regarding translation facilities may also be considered
320 a limitation to this review as only English language studies could be included.

321

322 **5.0 Conclusions**

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

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

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

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

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Figures

Figure 1 - Prisma Flow diagram



