
Objective: To evaluate the long-term effect on measures of forced vital capacity (FVC) before and after the introduction of regular lung volume recruitment (LVR) maneuvers (breath stacking) in individuals with Duchenne muscular dystrophy (DMD).

Design: Retrospective cohort study of pulmonary function data, including FVC, cough peak flow (CPF), maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP). Data were collected for 33 months prior to and 45 months after LVR introduction.

Setting: Ambulatory care in a tertiary level regional rehabilitation center in Canada.

Participants: All individuals (N=22) with DMD (mean age ± SD, 19.6±2.4y), who were prescribed LVR and reported adherence with therapy.

Interventions: Introduction of regular LVR (breath stacking); 3 to 5 maximal lung inflations (maximum insufflation capacity [MIC]) using a hand-held resuscitation bag and mouthpiece, twice daily.

Main Outcome Measures: Measures included the rate of decline of FVC in percent-predicted, before and after the introduction of regular LVR. Changes in maximum pressures (MIP, MEP, MIC), and cough peak flows were also measured.

Results: At LVR initiation, FVC was 21.8±16.9 percent-predicted, and cough peak flows were <270L/min (144.8±106.9L/min). Annual decline of FVC was 4.7 percent-predicted a year before LVR and 0.5 percent-predicted a year after LVR initiation. The difference, 4.2 percent-predicted a year (95% confidence interval, 3.5–4.9; P<.000), represents an 89% improvement in the annual rate of FVC decline.

Conclusions: The rate of FVC decline in DMD patients improves dramatically with initiation of regular LVR.

Key Words: Muscular dystrophy, Duchenne; Rehabilitation; Respiratory function tests; Vital capacity.

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RESPIRATORY COMPLICATIONS are the primary cause of morbidity and mortality in Duchenne muscular dystrophy (DMD) as progressive respiratory muscle weakness leads to hypoventilation1–3 and/or recurrent atelectasis and pneumonia,4,5 secondary to decreased cough effectiveness,6–12 Furthermore, it has been postulated that because of the decreased range of motion of the chest wall and lungs, stiffening of the ribcage may occur, reducing chest wall and lung compliance.13 Lung volume recruitment (LVR) (also known as breath stacking)12 is a means of stacking breaths by applying an inspiratory pressure, transmitted to the airways through an airtight facemask or mouthpiece, causing lung inflation, which is followed by a spontaneous or assisted forced expiratory maneuver.8,10,14,15 LVR achieves maximal lung insufflation capacity, expanding the chest wall and filling the lungs with air, so that an effective cough can be generated. In addition to improving cough efficacy and airway clearance, insufflation may also maintain chest wall range of motion and lung compliance16 by preventing atelectasis and contractures of the muscles of the thoracic cage.

The cough peak flow (CPF), a measure of cough capacity, achievable with the manual LVR technique, is 1.8 times greater than with an unassisted cough17,18 and is comparable with that obtained with a mechanical in-exsufflator.17,19–22 Furthermore, maximum insufflation capacity (MIC), the maximum volume of air that can be held in the lungs after breath-stacking, has been shown to improve, despite a decrease in vital capacity, over 0.5 to 24 years of follow-up in 282 patients with neuromuscular disease.23

A combination of the mechanical in-exsufflator and LVR, into an overall plan of care, has also been successful in some case series in avoiding hospitalization, pneumonia, episodes of respiratory failure, and tracheostomy.13,14,24–28 The precise contribution of LVR alone in these studies, however, is difficult to determine, because many treatment variables were simultaneously manipulated. A single cohort study13 of adults and children using LVR twice daily did demonstrate improvement in MIC and CPF over time.

The efficacy of LVR in slowing the progression of restrictive respiratory impairment, such as decline in forced vital capacity (FVC), has not been evaluated in long-term studies. As a result,
LVR has not been uniformly adopted as a treatment strategy.\textsuperscript{30,29,30} FVC is an important prognostic marker in DMD, which is routinely measured in clinical practice. The rate of decline of this pulmonary function variable predicts survival.\textsuperscript{31} Therefore, if the regular performance of LVR is able to slow the inevitable decline in FVC in this population, it would represent a significant clinical benefit, which may ultimately contribute to longevity. We hypothesize that long-term decline in FVC is attenuated by use of regular LVR therapy in individuals with DMD. The aim of this study was therefore to evaluate the impact on FVC of regular long-term use of LVR in individuals with DMD.

**METHODS**

All individuals with confirmed DMD at the Ottawa Hospital Rehabilitation Centre, for whom pulmonary function tests were available and who reported adherence with LVR, were included. Ethics approval was obtained from the Ottawa Hospital Research Ethics Board. LVR was administered by providing positive pressure, via tubing, and a mouthpiece, and was applied using a self-inflating resuscitation bag containing an inline 1-way valve.\textsuperscript{32} The number of breaths provided for LVR, per lung inflation, was determined by clinical evaluation consisting of visual inspection of chest wall excursion, patient comfort, and ability to hold a maximal volume. Positive pressure breaths were delivered in coordination with the patient’s own inspiratory effort, over 2 to 3 seconds. Three to 5 breaths were delivered in order to achieve an MIC for a total of 3 to 5 cycles, as tolerated. Illustrations of the patients’ own flow volume loop and MIC response were used to educate and encourage adherence with LVR (fig 1). LVR was prescribed twice daily. If secretions were present, a manually assisted cough (abdominal thrust) while the subject was at MIC was also recommended.

Retrospective analysis of pulmonary function data was carried out. Data were compared for a median of 33.5 months prior to the initiation of LVR treatment and a median of 45 months afterwards. Measures of spontaneous, unassisted FVC were obtained at each clinic visit during long-term follow-up.

The rate of FVC (percent-predicted) decline in the months before and after LVR initiation was compared.

**Measurements**

Spirometry was performed according to American Thoracic Society standards.\textsuperscript{55} Extended arm span, in centimeters, was used to estimate height in all patients. Measurements included FVC, CPF, maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP). FVC measurements were spontaneous and unassisted. MIC was measured after LVR and represented the largest volume achieved with LVR (see fig 1).

FVC and MIC values were measured using a spirometer (Profiler and CPSF/Db). Predicted values were those of the third National Health and Nutrition Survey (NHANES III).\textsuperscript{54} MIP and MEP were measured using a Micro RPM\textsuperscript{c} and predicted values were from Black and Hyatt.\textsuperscript{55} MEP was measured beginning at residual volume, and MIP was measured while at total lung capacity. Cough flows were measured using a peak flow meter (Mini-Wright\textsuperscript{d}).

**Statistics**

A piecewise linear mixed-effects regression model was used to analyze longitudinal measurements of FVC percent-predicted over time within individuals. The model included a parameter representing a change in the rate of decline of FVC percent-predicted at the introduction of LVR. A random intercept was used for each patient. The estimated rates of decline prior to initiation and after initiation of LVR were estimated, together with 95% confidence intervals (CIs). Statistical modeling was performed using R software version 2.13 (2011-04-13).\textsuperscript{36}

**RESULTS**

A total of 22 individuals were included in this study. Demographic features are described in table 1. Not all measurements were available for all patients at each assessment. At the time of LVR initiation, all participants had severe restrictive respiratory compromise (FVC, 21.8 ± 16.9%; percent-predicted, 1.0 ± 0.7L) and CPF below 270L/min (144.8 ± 106.9L/min), which is associated with decreased cough efficacy.\textsuperscript{17,37,38} All but 2 patients had a mechanical in-exsufflator available to them for use at home at times of respiratory infection. At the beginning of the study period 86% of patients were already using noninvasive ventilation (NIV). Two of the remaining 3 patients started NIV treatment during the study period, after the initiation of LVR. Four patients were receiving systemic steroids throughout the study period.

The trajectory of decline of FVC percent-predicted was substantially slower after the initiation of LVR (fig 2). Prior to the initiation of LVR, all patients had severe restrictive respiratory compromise (FVC, 21.8 ± 16.9%; percent-predicted, 1.0 ± 0.7L) and CPF below 270L/min (144.8 ± 106.9L/min), which is associated with decreased cough efficacy.\textsuperscript{17,37,38} All but 2 patients had a mechanical in-exsufflator available to them for use at home at times of respiratory infection. At the beginning of the study period 86% of patients were already using noninvasive ventilation (NIV). Two of the remaining 3 patients started NIV treatment during the study period, after the initiation of LVR. Four patients were receiving systemic steroids throughout the study period.

The trajectory of decline of FVC percent-predicted was substantially slower after the initiation of LVR (fig 2). Prior to
LVR the annual decline in FVC percent-predicted was estimated at 4.7 percent-predicted a year, and after initiation of LVR was 0.5 percent-predicted a year. The difference between the 2 rates was 4.2 percent-predicted per year, which was statistically significant ($P < 0.001$). This represented an 89% improvement in the rate of decline of pulmonary function per year.

A subgroup analysis was also performed, including only those patients with at least 2 FVC measurements pre- and post-LVR initiation. Refitting the piecewise linear mixed-effects model using this subset of patients produced similar results to those previously obtained (mean difference in annual rate of decline, 4.3 percent-predicted/year, $P < 0.001$). Figure 3 shows the individual FVC trajectories, with individual segmented regression fits to illustrate responses.

From Table 2 it is apparent that the inspiratory force, the MIP, declined by $3.8 \pm 7.3 \text{cmH}_{2}\text{O}$ ($P = 0.073$) and expiratory force, MEP, by $6.4 \pm 7.0 \text{cmH}_{2}\text{O}$ ($P = 0.005$). There was an insignificant fall in FVC of $-1.8 \pm 8.3$ percent-predicted ($P = 0.337$) and an increase in MIC of $1.8 \pm 11.9$ percent-predicted ($P = 0.51$) after LVR initiation. Both spontaneous and assisted CPF fell slightly by the end of the follow-up period.

**DISCUSSION**

Risk of respiratory failure in neuromuscular diseases is directly related to lung capacity. Untreated, survival below a vital capacity of 1L in DMD is 8% at 5 years. Lung capacity is also strongly related to the ability to cough and clear airway secretions. It follows, therefore, that maintenance of lung capacity may have a significantly positive effect on mortality. To our knowledge, this is the first study to identify the long-term effects of LVR on the decline of lung function in individuals with DMD. The introduction to and adherence with LVR techniques significantly improved the rate of decline of FVC in DMD patients compared with the rate of decline before LVR initiation.

It is known that the rate of pulmonary function decline accelerates in individuals with DMD in their teenage years and then becomes less steep in adulthood (after 18y of age), a phenomenon that was observed in our cohort and others. While a concurrent control group was not possible given the retrospective study design and the inclusion of LVR as a standard therapy at our institution, comparison can be made with a recently published study evaluating the natural history of lung function decline in a large international cohort of individuals with dystrophinopathies. This indicated that the rate of decline in FVC before age 19 was $-5.8 \pm 5.7$ percent-predicted per year ($95\%\ CI, -7.3$ to $-4.3$). Our data indicate a similar decline before LVR initiation of $-4.7\%$ ($95\%\ CI, -5.3$ to $-4.1$).
Restriction of lung volumes, as occurs in respiratory muscle weakening, is a passive therapy, not associated with long-term decline of FVC, however, is most likely related to improved muscle strength. In actuality, the improvements occurred from 144.8 to 232.8L/min. The mechanism of improvement in CPFs at initial introduction of LVR, and therefore significantly enhances CPFs. We have demonstrated improvement in CPFs at initial introduction of LVR, from 144.8 to 232.8L/min. The mechanism of improvement in the long-term decline of FVC, however, is most likely related to changes in compliance of the lung and chest wall, particularly because LVR is a passive therapy, not associated with muscle strengthening. In actuality, the improvements occurred in the presence of progressively weaker respiratory muscles. Restriction of lung volumes, as occurs in respiratory muscle weakness and shallow breathing, has been associated with decreased lung and chest wall compliance because of alterations in elastic tissues. In comparison, improvements in lung compliance have been demonstrated with 40cmH2O intermittent positive pressure breathing restricted patients with scoliosis. Even with pressures just 10cmH2O above the MIP in ALS using NIV, Lechtzin et al demonstrated small improvements in compliance. While a 17% reduction in MIPs and a 27% reduction in MEPs were observed, only a very small decrease was noted in the FVC after LVR initiation. This suggests an increase in respiratory system compliance, because substantially weaker respiratory muscles were capable of achieving a similar lung capacity.

Other studies have not confirmed an improvement in respiratory compliance with sessions of positive pressure breathing, suggesting that the decrease in lung compliance in those studies was because of a loss of lung volume, not alveolar surface tension or changes in tissue elastic properties. The differences between these studies and ours may be accounted for by the chronic, markedly lower lung volumes and progressive muscle dysfunction in our patients with DMD, which may involve different mechanisms for reduced compliance. Furthermore, in contrast to our population, most of these investigations were short-term, evaluated patients with much higher lung volumes and much lower pressures during positive pressure breathing than are used during LVR. The higher pressures and long-term use in patients with small lung volumes and continued muscle weakness are likely to lead to an even greater proportional increase in lung volume and therefore improvements in lung and chest wall mechanics.

No adverse effects of LVR were identified. Pneumothorax has been reported in 2 patients with DMD, associated with the use of mechanical in-exsufflation, and while the theoretical possibility of a pneumothorax exists, it has never been reported in the literature with manual insufflation, nor have we observed this in the treatment of hundreds of patients. The ability of the glottis to easily release or prevent any excessive volume likely eliminates the risk of barotrauma. In patients with spinal cord injury and sympathetic insufficiency, light-headedness is quite common with LVR, particularly if sitting upright, but we have never observed this in our patients with DMD, regardless of the presence or absence of significant cardiomyopathy.

**Table 2: Change From LVR Initiation to the End of Follow-Up**

<table>
<thead>
<tr>
<th>Pulmonary Function</th>
<th>n</th>
<th>Mean Change ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (%-predicted)</td>
<td>21</td>
<td>−1.2 ± 7.5</td>
<td>.456</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>21</td>
<td>0.0 ± 0.3</td>
<td>.583</td>
</tr>
<tr>
<td>MIC (%-predicted)</td>
<td>21</td>
<td>2.6 ± 11.7</td>
<td>.328</td>
</tr>
<tr>
<td>MIC (L)</td>
<td>21</td>
<td>0.1 ± 0.4</td>
<td>.151</td>
</tr>
<tr>
<td>CPF spontaneous (L/min)</td>
<td>18</td>
<td>−18.1 ± 62.2</td>
<td>.235</td>
</tr>
<tr>
<td>CPF with bag (L/min)</td>
<td>11</td>
<td>−18.8 ± 91.4</td>
<td>.514</td>
</tr>
<tr>
<td>MIP (cmH2O)</td>
<td>14</td>
<td>3.8 ± 7.3*</td>
<td>.073</td>
</tr>
<tr>
<td>MEP (cmH2O)</td>
<td>14</td>
<td>−6.4 ± 7.0*</td>
<td>.005</td>
</tr>
</tbody>
</table>

*Worsening.

--4.2%). These values are not significantly different (P= .18). After LVR initiation, however, the rate of decline in FVC in our group was markedly attenuated as compared with this published cohort of a similar age. The rate of decline in FVC percent-predicted in the published cohort was −3.0 ±3.4 percent-predicted a year (95% CI, −4.5 to 1.5) for the 23 individuals older than 18 years, compared with −0.5 percent-predicted per year (95% CI, −0.9 to −0.1) in our group. This difference of 4.2% (95% CI, 3.5– 4.9) represents an 89% reduction in rate of decline of FVC (P < .002), which is highly significant and clinically relevant.

Improved cough production is an immediate effect of LVR increasing FVC (MIC), which simply stores elastic energy in the lung and chest wall (at a volume above the intrinsic muscle capacity), enlarges airway caliber, places even weakened expiratory muscles at a slightly better length-tension relationship, and therefore significantly enhances CPFs. We have demonstrated improvement in CPFs at initial introduction of LVR, from 144.8 to 232.8L/min. The mechanism of improvement in the long-term decline of FVC, however, is most likely related to changes in compliance of the lung and chest wall, particularly because LVR is a passive therapy, not associated with muscle strengthening. In actuality, the improvements occurred in the presence of progressively weaker respiratory muscles. Restriction of lung volumes, as occurs in respiratory muscle weakness and shallow breathing, has been associated with decreased lung and chest wall compliance because of alterations in elastic tissues. In comparison, improvements in lung compliance have been demonstrated with 40cmH2O intermittent positive pressure breathing restricted patients with scoliosis. Even with pressures just 10cmH2O above the MIP in ALS using NIV, Lechtzin et al demonstrated small improvements in compliance. While a 17% reduction in MIPs and a 27% reduction in MEPs were observed, only a very small decrease was noted in the FVC after LVR initiation. This suggests an increase in respiratory system compliance, because substantially weaker respiratory muscles were capable of achieving a similar lung capacity.

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**Study Limitations**

Because this study consisted of a retrospective cohort, a few limitations have been variable. In patients with ALS, Kleopa et al demonstrated a small improvement in the rate of decline of FVC in a small portion of study participants, but of a considerably lesser magnitude (27%) than that demonstrated in our study of DMD patients (89%). In other studies in ALS and in a study of children with neuromuscular disease, in whom NIV was introduced over a 1-year period, no improvement in FVC decline was demonstrated. All but 3 of the 22 individuals in the current study were already using nocturnal NIV before the introduction of LVR. Two patients started NIV during the course of the study. The only 2 who began NIV after LVR demonstrated no additional evidence of a diminished rate of decline in FVC. As such, NIV was unlikely to be an important influence on the subsequent rate of decline in FVC in those patients. Therefore, it is likely that LVR alone was responsible for the improvement in the decline of FVC.

Some additional therapies were not specifically evaluated in this study, but were not thought to change significantly during the course of the study. Almost all of our patients had access to a mechanical in-exsufflator for use at times of respiratory exacerbation, but this access was no different before or after the introduction of regular LVR and should not have affected the decline in FVC, particularly when it was used for short periods of time. Furthermore, the pressures achieved with the mechanical in-exsufflator are substantially lower (40cmH2O) than those commonly attained with manual insufflation. Inline measurements of pressure during LVR ranged from 45 to 60cmH2O (personal observations).

Steroid use is also important, because steroids have been shown to affect the decline in lung function. However, in this study, only a small number of patients (n=4) were using steroids and did so throughout the study period.

**Implications**

Airway clearance strategies, such as mechanical in-exsufflation, have been recommended in some care guidelines for patients with neuromuscular disease, including DMD. Mechanical in-
exsufflation has not been uniformly adopted; however, because of its high cost (minimum $3000Cdn) and because its evidence of benefit is limited to observational data. Several groups have called for additional studies before adopting it into routine care.\textsuperscript{10,29,30,51}

In contrast, the minimal cost of a self-inflating resuscitation bag with a 1-way valve ($75Cdn) and the simplicity of this treatment make this therapy very appealing, even for impoverished areas of the world where access to expensive therapies may be limited.

Given the dramatic improvement in CPF and the long-term rate of decline of pulmonary function demonstrated in this study after initiation of LVR, this therapy has significant clinical benefit in DMD and potentially other neuromuscular diseases. Although our results suggest an independent, therapeutic benefit of LVR, a prospective, randomized, controlled study would provide much stronger evidence and would exclude with greater certainty any adverse effects not identified in this observational study. As long as access to effective mechanical in-exsufflation during exacerbations was ensured, a randomized controlled trial of LVR would be ethical and could provide insight into additional effects of LVR, such as improved quality of life and hospitalization rates. More research is needed to address these questions for this promising therapy, so that it can be more widely adopted into practice in treating this population.

CONCLUSIONS

The rate of FVC decline improves dramatically with initiation of regular LVR in DMD patients.

Acknowledgment: We thank Christie O’Connell, BSc for her assistance in collecting and managing the data.

References


Suppliers
a. Lung Volume Recruitment Kit; Trudel Medical Marketing Ltd, 758 Third St, London, ON N5V 5J7, Canada.
c. Micro Medical Ltd, The Crescent, Jays Close, Bassingstoke RG22 4BS, UK.
d. Mini-Wright Peak Flow Meter; Clement Clark International Ltd, Edinburgh Way, Harlow, Essex CM20 2TT, UK.