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ORIGINAL ARTICLE

Lung volume recruitment in patients with Duchenne Muscular Dystrophy in the early non-ambulatory stage

Reclutamiento de volumen pulmonar en pacientes con Distrofia Muscular de Duchenne en etapa no ambulatoria temprana

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What do we know about the subject matter of this study?

Patients with Duchenne muscular dystrophy (DMD) experience a progressive decrease in pulmonary function with loss of ambulation. The decline in vital capacity leads to morbidity and mortality due to ventilatory failure and ineffective cough.

What does this study contribute to what is already known?

Lung volume recruitment at home has a favorable impact on vital capacity, maximum insufflation capacity, and cough capacity in patients with DMD in the early non-ambulatory stage, with no expected decline in lung function after 12 months of follow-up. This is the first evidence reported in Latin America using this low-cost rehabilitation strategy.

Abstract

Ventilatory and cough insufficiency are the main causes of morbidity and mortality in patients with Duchenne muscular dystrophy (DMD). Lung volume recruitment (LVR) might decrease the decline in vital capacity (VC). **Objective:** To determine the changes produced by respiratory training performed at home with LVR techniques and manually assisted cough on VC, maximum insufflation capacity (MIC), and peak cough flow (PCF) in adolescents with DMD in the early non-ambulatory stage. **Patients and Method:** Quasi-experimental study with repeated measurements every three months. 16 adolescents with DMD close to the CV plateau and cough insufficiency were evaluated and trained daily in LVR and assisted cough, with follow-up for 12 months, assessing respiratory function, quality of life, and caregiver overload. **Results:** Eleven users (69%), aged 12.7 ± 2.8 years, completed

Keywords:
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the follow-up. Supine position VC and PCF + compression increased significantly (p = 0.047; p = 0.012, respectively). Seated VC and MIC tended to improve by 11.2% and 21.6%, respectively. Quality of life and caregiver overload did not present significant changes. **Conclusion**: In adolescents with DMD in the early non-ambulatory stage, significant improvements were observed in VC and cough capacity. This provides an intervention of easy implementation, capable of preventing the expected respiratory functional decline.

Introduction

Duchenne muscular dystrophy (DMD) is the most common neuromuscular disease in children[1]. Its natural course results in progressive muscle weakness and loss of ambulation between the ages of 7 and 14 years, with the subsequent decline in vital capacity (VC)[2,3]. The main cause of morbidity and mortality in patients with DMD is ventilatory failure secondary to respiratory muscle weakness and ineffective cough[4-7]. The combination of reduced cough function, inspiratory capacity, and VC[8] leads to microatelectasis, where the primary determinant of reduced lung volume is a decrease in thoracic pulmonary compliance rather than a reduction in respiratory muscle strength[7,9,10-12]. The literature shows that initiating lung volume recruitment (LVR) during non-ambulatory stages, after reaching the VC plateau, can shift the maximum slope of functional decline over 5 years[9].

The early non-ambulatory stage is defined by loss of ambulation and preservation of upper extremity function, wheelchair mobility, and maintenance of head control. Increased sitting time and progressive axial muscle weakness favor the development of scoliosis. Given the motor and ventilatory pump compromise, during this stage, the VC and cough plateau are reached before the respiratory functional decline[13-15].

Once this plateau is reached, VC decreases with a steeper slope of decline in patients with DMD (5-10% per year), compared to persons without this pathology (1-1.2% per year)[9,16]. In general, the degree of VC loss is about 6.3% per year from 10 to 20 years of age, but it is greater in those who lose ambulation earlier and with VC plateaus measured in lower absolute values[16]. Thus, the earlier ambulatory capacity is lost, the faster the deterioration and slope of decline in VC[7,15,16]. VC values below 50% of predicted or less than 2 L correlate with ineffective cough (< 270 L/min). Below this threshold, there is a high risk of developing pneumonia and ventilatory failure[17]. Clinical management guidelines and analysis of retrospective studies indicate that this risk decreases with the incorporation of manual and/or mechanical assisted cough maneuvers[5,7,9,10,18,19]. The addition of LVR to the treatment has also been shown to prolong survival by avoiding ventilatory failure, endotracheal intubation events, extubation failures, and tracheostomies[7,10,18].

Non-invasive respiratory care is a tool that improves pulmonary function and reduces predisposition to airway infections, improving quality of life[20] and increasing survival in people with DMD[10]. The relationship between respiratory function parameters and the aspects evaluated by quality-of-life questionnaires suggests that any change that improves respiratory function would also improve the well-being of patients[20].

Thus, it is possible to hypothesize that, even though DMD is a progressive disease, respiratory rehabilitation would improve quality of life, and clinical and functional status[10]. This would justify incorporating active LVR protocols with a manual resuscitation bag[17] and assisted cough maneuvers as standard of care in the described population, which has no previous experience with respiratory rehabilitation.

The objective of this research is to determine the changes produced by daily home LVR during 12 months of intervention and follow-up, on VC, maximum insufflation capacity, cough capacity, quality of life, and caregiver overload in patients with DMD in early non-ambulatory stage in a Chilean population.

Patients and Method

Study design

Quasi-experimental design study with repeated measurements every 3 months to patients with DMD in the early non-ambulatory stage, during a 1-year intervention and follow-up period.

The patients met the following inclusion criteria: children and young people with a confirmed diagnosis of DMD older than 6 years of age in regular follow-up at the *Instituto Teletón Santiago*, in the early non-ambulatory stage according to the classification made by a physiatrist, with a sitting VC less than the lower limit of the theoretical predicted according to the Global Lung Function Initiative[21]. Exclusion criteria included patients who at the time of the initial evaluation were not able to understand and/or follow instructions, caregivers unable to perform the LVR procedures, and those who did not agree to participate in the follow-up.

Ethical aspects

Informed consent forms were requested from patients aged 18 years and older, from caregivers of children under 18 years, and informed assent from adolescents aged 12 to 17 years. The project was approved by the SPANL-*Teletón* Scientific Ethical Committee (Act 118/18-08-2021).

Patient selection

After a review of the medical record, 123 patients met the diagnosis of DMD at the *Instituto Teletón Santiago*, of which 40 patients were in the functional stage described. Of this group, 38 attended the initial respiratory evaluation. Those who met the inclusion criteria were invited to participate in the research, incorporating a total of 16 patients (Figure 1). Those who did not meet the criteria or did not agree to participate continued in the current respiratory program, without detriment to their care.

During the follow-up period, 5 patients left the program, of which 3 presented low adherence and non-compliance with follow-up and care (absenteeism without justification to the scheduled in person and telemedicine), 1 due to illness of the main caregiver, and 1 moved abroad. This resulted in explicit refusal to participate in the study, with the impossibility of maintaining its continuity, ending a total cohort of 11 patients.

Intervention and follow-up

The patients entered a protocol that included a baseline assessment and two training sessions (Appendix 1, available in the online version). In the training, educational routines were established through demonstrations of the active LVR technique and manual assisted cough maneuvers, developed by physical therapists previously trained under the same conditions. These routines were then performed by the caregivers under supervision until they achieved the competencies for their complete independent execution, under the standards described in the literature[7,12,17,22] (Figure 2). After the training, the caregiver was instructed to apply the techniques at home daily, with at least 40 repetitions per day[17,18].

As a validation criterion, a maximum of one week was considered as the time between the initial evaluation and the start of training. Once the training was completed, during the home intervention stage, weekly telemedicine follow-up was carried out through telephone contact and video calls for the first 3 months. Subsequently, video calls were continued every two weeks until the end of the study. In the follow-up sessions, the execution of the technique was evaluated with a common and standardized clinical criterion of the maneuver, through a checklist with 9 items for the active LVR and manual assisted cough maneuvers, with dichotomous response (yes/no), applied to each child by the three evaluating physical therapists in the scheduled check-up sessions. Based on this form, the concordance between observers was evaluated (Appendix 2, available in online version). In parallel, intermediate evaluations were carried out every 3 months, and a final evaluation with the same characteristics as the first evaluation after 12 months of intervention.

The initial and final evaluation included an anamnesis and a clinical record review, where sociodemographic characteristics were collected (age, age at loss of ambulation, socioeconomic status years without ambulation, weight, arm span) and clinical history (scoliosis, spinal surgery, cardiac history, respiratory conditions, check-up with pneumologist belonging to Chilean non-invasive ventilatory assistance at home program, type of mutation, use of corticosteroids, training, and hospitalizations). In addition, a respiratory evaluation was carried out (sitting and supine VC, maximum insufflation capacity (MIC), and peak cough flow (PCF), with compression, and from MIC) (Appendix 1); application of the PedsQL neuromuscular module version 3.0 (5-18 years)[23] and the Zarit caregiver burden scale[24,25].

The evaluations were performed by three physical therapists under the same standards of environment, physical space, and implementation, with a detailed description of the evaluation procedure. This evaluator was different from the physical therapist who performed the training, intervention, and follow-up of each of the patients.

Variables

Dependent variables were identified as those derived from the assessment of respiratory function (sitting and supine VC, MIC, and PCF with compression, and from MIC), health-related quality of life, and caregiver overload. Descriptive variables were age at the start of the study, age at loss of ambulation, years without ambulation, weight, arm span, socioeconomic status, and comorbidities.

The evaluation of lung volumes contemplated the measurement of VC and MIC. A circuit composed of the Wright™ and the Haloscale™ respirometer, antibacterial/viral filter, and inflatable face mask sized according to the patient was used. VC was measured while sitting and supine position. The MIC measurement was performed while sitting, following active LVR with a respiratory kit (bag-valve-mask, one-way valve, and patient interface).

The cough capacity was measured in three different tests:PCF, PCF with abdominal compression, and PCF from MIC. For the measurements, a Mini-Wright

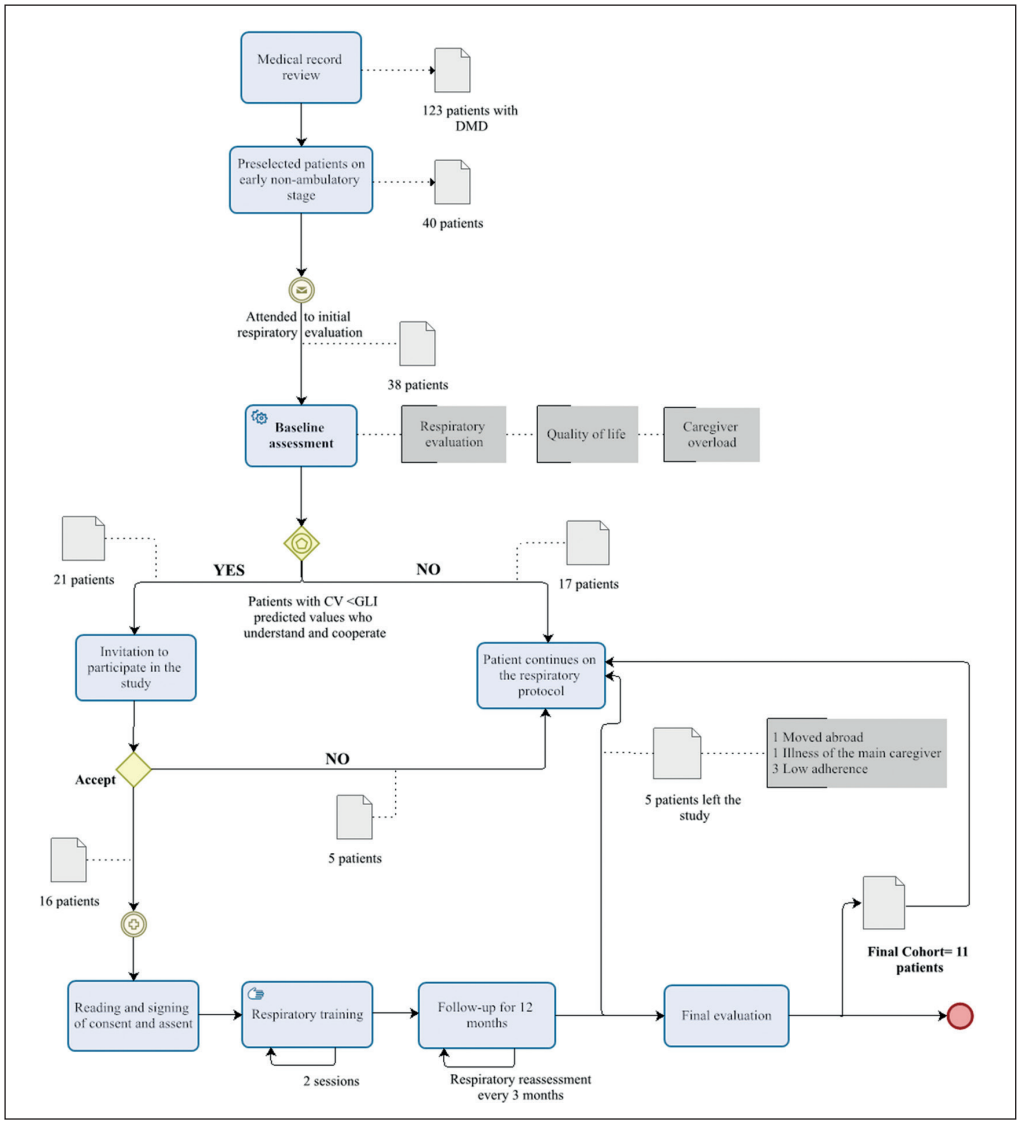

Figure 1. Flowchart for patient selection, intervention and follow-up in Duchenne Muscular Dystrophy patients.

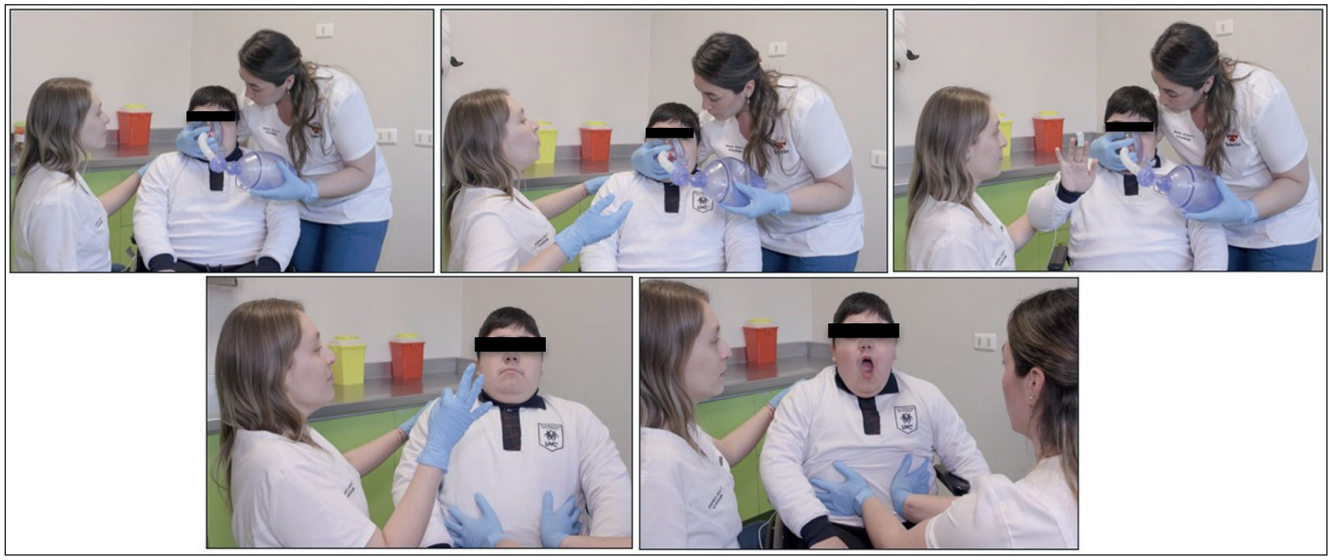

Figure 2. Description of active lung volume recruitment maneuver with manual resuscitation bag and manual cough facilitation.

peack flow meter was used together with a nasal-oral interface, with the patient seated. The highest value obtained from three attempts at each of the pulmonary function tests was recorded.

Health-related quality of life was assessed through the PedsQL 3.0 neuromuscular module, validated for DMD in its original version[26], in Spanish[27], and translated into Chilean Spanish for its use and application in children with neuromuscular disease aged between 5 and 18 years[23,28]. The questionnaire was self-administered by the patient and her/his caregiver and is composed of three dimensions ("about the neuromuscular disease", "communication", and "about our family resources"). The answers are a Likert-type scale with five options from 0 (never) to 4 (almost always); the scores are transformed into an inverse scale from 0-100, being 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0. The total is obtained by adding the averages of the scores of all the dimensions. Higher scores indicate a better perception of quality of life[29].

Caregiver overload was assessed with the questionnaire validated in Chile. The questionnaire consists of 22 Likert-type scale questions with 5 options (1-5 points), the results of which are summed into a total score (22-110 points). This score classifies the caregiver into: "no overload" (≤ 46), "light overload" (47-55), or "intense overload" (≥ 56). "Light overload" represents a risk factor for generating "intense overload"[25].

Statistical analysis

The data extracted from medical records and questionnaires were recorded in an Excel spreadsheet and processed using SPSS v.17. Summary measures of central tendency and dispersion were obtained. For the dependent variables VC, MIC, and PCF, normality assumptions were verified using the Shapiro-Wilks test, and sphericity was assessed with Mauchly's test. Since normality was not confirmed for all dependent variables, the non-parametric Friedman test was used. The percentage change from the baseline value of MIC and sitting VC was calculated.

To verify the influence of characteristics such as age, age at loss of ambulation, years without ambulation, weight, and arm span on the PCF, the Wilcoxon test was used, comparing all follow-up results to baseline measurements.

The Wilcoxon test was used to compare baseline and final quality of life and caregiver overload. In all the tests used, a $p < 0.05$ value was considered significant.

The intraclass correlation coefficient[30] was used to obtain the inter-rater agreement. Results were expressed as mean ± SD. A $p < 0.05$ value was considered significant for all the tests used.

Results

Eleven patients (11/16; 69%) completed the intervention and follow-up. At initial evaluation (n = 16), age was 12.7 ± 2.8 years and age at ambulation loss 10.1 ±1.9 years. 13 patients were on oral glucocorticoid therapy, 3 were on nocturnal noninvasive ventilation, 3 had scoliosis, and one of them underwent posterior arthrodesis. Table 1 shows the sociodemographic characteristics.

The inter-rater agreement was 0.76 (0.42-0.93; $p < 0.001$). The system excluded 4 cases with missing data. At baseline assessment, the median values of PCF and PCF + abdominal compression were 230 L/min and 210 L/min, respectively, being under the cough threshold of 270 L/min. The sitting MIC-VC difference was 0.26 L (Table 2).

There was significant improvement in the variables of supine VC ($p = 0.047$) and PCF + abdominal compression ($p = 0.012$). Although the other respiratory function variables did not show significant variations, sitting VC, and MIC presented a percentage change in their medians of 11.2% and 21.6%, respectively, at the end of the study.

There are significant influences on PCF in controls 2, 3, and 5 when age is ≤ 13 years, they present ≤ 2 years without ambulation and an arm span < 149 cm (Table 3).

There was no significant change in the quality of life between the baseline and final assessment according to parents and patients ($p = 0.722$ and $p = 0.374$, respectively). In the measures administered to parents, the baseline results reported "poor health-related quality of life" (65 points), while the final results were "poor health-related quality of life" (73 points). In patients, the baseline and final results remained in the "poor health-related quality of life" classification, with median baseline values of 77 and final values of 74 points.

In the caregiver overload assessment, there was no significant change between the baseline and final assessment ($p = 0.721$); its median baseline and final (38 points and 39 points, respectively) maintained its classification in "no overload".

Discussion

Our results suggest that LVR and assisted cough maneuvers for 12 months significantly improved supine VC and cough capacity in adolescents with early non-ambulatory DMD, around the VC plateau and ineffective cough. In addition, sitting VC tended to improve, although a decline over the years is to be expected[16,31].

Table 1. Sociodemographic characteristics of patients with Duchenne muscular dystrophy at baseline

Characteristics		n	%
Total		16	100.0
Socioeconomic status	Upper	1	6.3
	Upper middle	5	25.0
	Lower middle	5	31.3
	Lower	4	18.8
	Unspecified	1	12.5
Age (years)	≤ 10	3	18.8
	11-13	5	31.3
	14-16	8	50.0
Average ± DS*	12.7 ± 2.8		
Age at loss of ambulation (years)	≤ 8	3	18.7
	9-10	6	37.5
	11 and older	7	43.8
Average ± DS	10.1 ± 1.9		
Years without ambulation	≤ 2	8	50.0
	3-6	8	50.0
Average ± DS	2.6 ± 2.1		
Weight (kg)	≤ 40	6	37.5
	40-50	4	25.0
	51 and older	6	37.5
Average ± DS	53.8 ± 21.0		
Arm span (cm)	≤ 130	4	25.0
	131-149	5	31.2
	150 and older	7	43.8
Average ± DS	147.8 ± 19.4		

* SD: Standard Deviation

LVR rapidly increases lung compliance and VC[7,11,32-35], reducing work of breathing and achieving better cough flows given the increase in lung elastic recoil pressures[9]. The MICis an indirect measurement of pulmonary compliance that has been widely used in the studies of Bach et al[9,17-19,36-38], specifying that even when VC declines, the difference between MICand VC (MIC-VC) is maintained or improved. This is consistent with the results obtained in our cohort. The MIC, the result of active LVR, is only possible in patients with neuromuscular disease without significant involvement of innervated bulbar muscles, as is the case of patients with DMD at this stage of the disease[7,37]. In the study population, three patients were included in the national noninvasive ventilation program, who did not present significant differences in changes in supine VC and PCF + abdominal compression compared with patients without noninvasive ventilation. These patients may have had a VC > 10mL/kg and VC > 1L at the initial evaluation, which is considered adequate pulmonary compliance[13,15,39].

LVR has been widely demonstrated to be effective in DMD and other neuromuscular diseases[9,17,18,31-34]. Our study is the first in Latin America to report similar results in the described population and is consistent with studies that demonstrate the impact of active LVR in patients with DMD in a comparable clinical and functional respiratory situation. This reaffirms that it delays the decline slope of VC[9], as does the study by McKim et al, which included patients with markedly decreased VC values as predicted[12]. Crescimanno et al. reported that supine VC and PCF + compression

Table 2. Assessment of respiratory function of patients with Duchenne muscular dystrophy during 12 months of respiratory training and follow-up (n = 11)

Variable	Follow up										P-value: Friedman's test (n = 11)
	Baseline 1		Control 2		Control 3		Control 4		Control 5		
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
Sitting VC (L)	1.78	0.68	1.85	0.91	1.87	1.06	1.95	1.02	1.98	1.03	0.062
Supine VC (L)	1.59	0.91	1.69	0.64	1.85	0.97	1.78	0.95	1.72	0.61	**0.047***
MIC (L)	1.90	0.71	2.02	1.12	2.19	1.15	2.2	1.12	2.31	1.16	0.120
Sitting MIC-VC (L)	0.26	0.37	0.17	0.36	0.27	0.30	0.14	0.39	0.23	0.25	0.623
PCF (L/min)	230	130	250	140	260	110	240	140	260	100	0.056
PCF + Compression (L/min)	210	110	250	100	250	110	240	120	250	110	**0.012***
PCF + MIC (L/min)	240	140	250	100	240	120	250	140	260	110	0.078
% change median MIC	-		6.3		15.3		15.8		21.6		
% change median sitting VC	-		3.9		5.1		9.6		11.2		

MIC: Maximum insufflation capacity; VC: Vital capacity; PCF: Peak cough flow; SD: Standard Deviation
*Significant. Baseline 1, prior to intervention; 2-5 controls; controls performed every 3 months for 1 year of follow-up

Table 3. Influence of demographic and anthropometric factors on peak cough flow compared to baseline measurements

Outcome variable	Factor	Category	Seguimiento			
			Control 2	Control 3	Control 4	Control 5
Pico flujo tos basal	Age	≤ 13 years old	0.023*	0.034*	0.104	0.041*
		14 years and older	0.033*	0.175	0.068	0.496
	Weight	≤ 49.0 kg	0.040*	0.088	0.197	0.066
		49,1 kg and above	0.019*	0.089	0.043*	0.246
	Age at loss of ambulation	≤ 10 years old	0.011*	0.061	0.104	0.045*
		11 years and older	0.106	0.088	0.066	0.45
	Years without a ambulation	≤ 2	0.013*	0.034*	0.058	0.041*
		3-6	0.058	0.175	0.109	0.496
	Arm span	< 149	0.025*	0.020*	0.058	0.027*
			0.031*	0.343	0.109	1.000

*p < 0.05

are dependent variables of thoracic cage compliance, expiratory muscle activity, and diaphragm function[20]. Besides, Sheers et al. point out that in DMD, the progressive affectation of motor and diaphragmatic involvement generates a decrease in the supine VC compared to the sitting VC, which is clinically supported by physiological alterations during sleep[11].

Although the recruited volumes, expressed as the MIC-VC difference, were lower than those reported in longer follow-ups[9], if maintained over time, it suggests that the projection of active LVR training could have favorable results, improving thoracic pulmonary compliance and reducing work of breathing. At the same time, increasing supine VC volumes could have an impact on the late onset of nocturnal hypoventilation and hypercapnia, which impacts negatively on survival[11].

Respiratory muscle weakness not only affects VC but also cough capacity; the improvement obtained in the variable PCF + abdominal compression is a clinically significant result considering that the decrease in functional cough is a relevant risk factor[9]. Giménez et al. reported that, in order to achieve an effective cough in patients with neuromuscular disease, it can be manually assisted (LVR + abdominal compression), a situation that is clinically explicable when functional cough thresholds (> 270 L/min) are exceeded[39]. Other studies in patients with DMD reported significant changes in PCF values after performing LVR + manual assisted cough maneuvers, reinforcing the impact of this technique[7,34].

Regarding the evaluation of quality of life, a positive trend in the parents' perception stands out. The small difference in the perception of patients has already been reported by other authors. Kohler et al. found no relationship between quality of life and respiratory function in patients with DMD[40]. However, Ahlstrom et al. stated that there is a relationship between them in individuals with inherited muscular dystrophy in more advanced stages[41]. Therefore, our results could be associated with the functional stage in which the studied patients were, with the understanding that there is greater motor and respiratory involvement as the disease progresses. Caregiver's overload also showed no significant changes during 1 year of follow-up. This finding could be related to the fact that the intervened population had a shorter caregiver dependence time, as other studies in DMD clarify that the source of the burden is specifically related to the caregiving time and not to the degree of functional independence loss[42]. In addition, our study incorporated a standardized measurement of caregiver overload, which other reported experiences have not used[33].

The small number of patients included and the loss to follow-up are perceived as limitations of the study and encourage new studies with a larger number of patients and long-term follow-up, in order to observe the effect on the decline slope of VC, as has been previously reported by other authors[7,9,12,33]. The absence of a control group is not seen as a limitation, due to the ethical imperative of not being able to subtract patients from respiratory rehabilitation that already had known favorable results. On the other hand, the concordance between evaluators was high, which shows that the uniformity in the maneuvers designed avoided a source of bias in the procedure[30]. Sleep studies or noninvasive trend monitoring through oxy-capnography follow-up were discouraged, given that none of the patients had waking baseline SpO2 below normal, did

not report symptoms of nocturnal hypoventilation, and had VC values > 1L. These characteristics make it unlikely that noninvasive ventilatory support was required[39].

In conclusion, in patients with DMD close to the vital capacity plateau and ineffective cough, intervened with LVR plus assisted cough maneuvers during 12 months of follow-up, significant improvement in supine VC and cough capacity was observed. The observed results support the incorporation of the evaluation, prescription, and training of LVR in patients with DMD in an outpatient setting, reinforcing the approach of implementing new daily rehabilitation routines that do not overload patients or families.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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