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ANALYZING RESPIRATORY MUSCLE WEAKNESS AND THORACOPULMONARY RESTRICTION IN SUBJECTS WITH DUCHENNE MUSCULAR DYSTROPHY

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Abstract **Objective**: To analyze the underlying components of reduced maximal static inspiratory (MIP) and expiratory (MEP) pressures in subjects with Duchenne muscular dystrophy. **Methods**: Forty-three subjects were assessed based on routine pulmonary function tests. MIP and MEP were measured the subjects performed maximal expirations and inspirations using a snorkel mouthpiece. Lung volumes were measured using the helium dilution technique. **Results**: The mean age was 13 years (range, 7-20 years). Median total lung capacity (TLC) and residual volume (RV) were 78.0 (49.0-94.0) and 27.0 (19.7-30.1) of the predicted values respectively. The RV/TLC relationship was 35.3% (28.1-47.7). Thirty-five subjects had a TLC below the lower limit of normal, while 31 had an RV/TLC ratio above the upper limit of normal. The median (IQR) MIP and MEP values were -53.0 (-65.5 to -41.8) and 58.0 (41.5-74.8) cmH_2O respectively. MIP and MEP in percent of the predicted values (predicted TLC and RV) were 42.6 (33.3-50.8) and 33.7 (23.9-44.5). MIP in percent of the RV reached for Group A (7-11 years old) was higher (p 0.025) while MEP in percent of the TLC reached for Group B (12-16 years) and C (17-20 years) were higher too (0.031). **Conclusions**: In subjects with Duchenne muscular dystrophy, the intrinsic weakness of respiratory muscles and mechanical disadvantage lead to inadequate maximal static pressure generation. Maximal static pressures should be interpreted cautiously as they overestimate respiratory muscle weakness when compared to predicted values obtained at TLC and RV. Our results provide additional data supporting absolute values use rather than predicted values.

Key words: Duchenne muscular dystrophy, respiratory muscles, maximal respiratory pressures, muscle weakness, neuromuscular diseases

Resumen ***Análisis de la debilidad de los músculos respiratorios y de la restricción toracopulmonar en sujetos con distrofia muscular de Duchenne***

Objetivo: Analizar los componentes subyacentes de las presiones inspiratorias (MIP) y espiratorias (MEP) estáticas máximas reducidas en sujetos con distrofia de Duchenne (DMD). **Métodos**: Se evaluaron 43 pacientes mediante pruebas de función pulmonar rutinarias. MIP y MEP fueron medidas a inspiración y espiración máximas. Los volúmenes pulmonares se midieron mediante dilución de helio. **Resultados**: Edad media 13 años (rango 7-20 años). La capacidad pulmonar total (TLC) y el volumen residual (RV) fueron 78.0% (49.0-94.0) y 27.0% (19.7-30.1) de los valores predichos. El RV/TLC fue de 35.3% (28.1-47.7). Treinta y cinco sujetos tenían una TLC por debajo del límite inferior de normalidad, 31 tenían una RV/TLC por encima del límite superior de la normalidad. MIP y MEP fueron -53.0 (-65.5 a -41.8) y 58.0 (41.5-74.8) cmH_2O, mientras que en % de los predichos (TLC y RV predichos) fueron 42.6 (33.3-50.8) y 33.7 (23.9-44.5). MIP en % del RV alcanzado (Grupo A 7-11 años) fue mayor (p 0.025), y MEP en % de la TLC alcanzada Grupo B (12-16 años) y C (17-20 años), también fue mayor (0.031). **Conclusiones**: En sujetos con DMD, debilidad intrínseca de los músculos respiratorios y desventaja mecánica conducen a generación de presión estática máxima inadecuada. Las mismas deben interpretarse con cautela, ya que sobrestiman la debilidad de los músculos respiratorios si se las compara con las tablas de valores predichos obtenidos a TLC y RV. Nuestros resultados proporcionan datos adicionales que respaldan la utilización de valores absolutos en lugar de los predichos.

Palabras clave: distrofia muscular de Duchenne, músculos respiratorios, presiones respiratorias máximas, debilidad muscular, enfermedades neuromusculares

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KEY POINTS
Current knowledge

- Respiratory muscle weakness in Duchenne dystrophy is due to the degenerative myopathic process of the disease. Although known, the dependence on the lung volume at which the maximal inspiratory and expiratory maneuvers are performed is often not considered. It can lead to misinterpretation, especially when relating the generated pressure as a percentage of the predicted values.

Contribution of the article to current knowledge

- In subjects with Duchenne muscular dystrophy, intrinsic respiratory muscle weakness and mechanical disadvantage lead to inadequate peak static pressure generation. Our results suggest that these values should be interpreted cautiously, as they overestimate respiratory muscle weakness compared to the predicted values obtained in TLC and RV. Our results provide additional data supporting absolute values use rather than predicted values.

Duchenne muscular dystrophy (DMD), an X-linked disorder, affects one in 5,000 boys and presents proximal muscle weakness in early childhood. Untreated boys become wheelchair users by the age of 12 years and die of cardiorespiratory complications in their late teens to early 20s[1, 2]. With current medical advances, many DMD patients can now expect to live into their forties[3]. It is characterized by progressive loss of skeletal muscle strength, respiratory muscle weakness, and respiratory failure. In addition, lung volumes are almost invariably diminished due to respiratory muscle weakness and progressive thoracic deformities[4].

Measurement of respiratory function and muscle strength are part of its routine assessment, allowing clinicians to predict which patients will require assisted coughing and ventilation[5-7]. Spirometry, specifically forced vital capacity (FVC), is a simple measure of lung function and can help predict certain features of clinical outcomes. However, it is nonspecific and fails to distinguish inspiratory from expiratory muscle weakness and restrictive syndromes caused by chest wall or parenchymal abnormalities[8-10].

Maximal static pressures measurement at the mouth is a simple test that allows quantification of inspiratory and expiratory muscle strength. However, it depends not only on muscle strength but also on the elasticity of the thoracopulmonary system. Thus, in normal subjects, maximal inspiratory pressure (MIP) is reached at residual volume (RV), and can decrease as a consequence of expiratory weakness, preventing RV from being reached. In contrast, maximal expiratory pressure (MEP) is achieved at total lung capacity (TLC) and can decrease if weakened inspiratory muscles cannot inflate lungs up to TLC[11].

In DMD, low MIP and MEP values may result from muscle weakness and low lung volumes. However, interpretation of MIP and MEP, intrinsic factors and operative lung volume have not been specifically reported. Therefore, the present study objective was to compare maximal static pressures in subjects with DMD concerning the static lung volumes at which MIP and MEP manoeuvres were performed. The implications of using predicted values at TLC and RV could be relevant and may allow for an alternative interpretation of respiratory muscle weakness in DMD patients.

Materials and methods

Subjects

A retrospective search was made on our database for DMD patients that had performed spirometry, lung volumes determination and measurement of maximal static respiratory pressures. Diagnosis was based on a combination of clinical findings, muscle enzyme levels, electromyogram and muscle biopsy, as well as DNA testing, when available. Clinical status and motor functional capacity (MFC) were gathered from clinical records for each patient[12]. Pulmonary function testing manoeuvres were reviewed and those patients whose tests didn´t fulfil acceptability criteria were excluded. Since most patients were in a wheelchair or had spinal deformities, armspan was used to estimate subject's height. In those with upper extremity contractures, the sum of each arm segment was used[13,14].

Pulmonary function testing

Spirometry was performed with a volumetric spirometer, according to the standard method and lung volumes were measured with the helium dilution technique (Collins GS-PFT, Warren E. Collins, Inc. Braintree, Massachusetts, USA) using standard methodology[15, 16]. Maximal static pressures at the mouth (MIP and MEP) were measured according to standard methodology using a flanged mouthpiece connected to a pressure transducer (MP45, Valydine Engineering, Northridge, CA, USA). MIP was performed by having subjects emptying their lungs as much as possible and then perform a maximum inspiratory manoeuvre; MEP was performed by having the subjects inspire maximally and then perform a maximum expiratory manoeuvre[17]. The values were digitally recorded (MP100 Workstation, BIOPAC Systems Inc, Goleta, CA, USA).

Measurements are expressed in absolute values and as percent of predicted values[16, 18]. Cook et al. values for MIP and MEP at different lung volumes were used to establish a comparison with expected pressures at actual lung volumes achieved for three age-matched subgroups[19]. According to Cook, the diagrams pressure volumes were created as follows: Group A: 7-11 years, Group B: 12-16 years and Group C: 17-20 years[19].

Statistical analysis

Mean and standard deviation or median values and interquartile ranges are reported according to distribution. Student's

t-test and analysis of variance were done according to distribution for comparisons.

The study was approved by the local Institutional Review Board, protocol #216, CUDAP-TRI-UBA 0051153/2018.

Results

Data from 43 DMD patients (range 7-20 years) were analyzed: Group A, n = 15; Group B, n = 19; Group C, n = 9. Anthropometric, clinical and functional characteristics are summarized in Table 1. Twenty-one subjects were MFC grade 9 and 10 (subject in a wheelchair, elbows flexed in the anti-gravity position or unable to move against gravity). Thirty-five subjects exhibited TLC below the lower limit of normality, while 31 had RV/TLC ratio above the upper limit of normality.

Figure 1 shows the relationship between lung volumes and maximal static pressures (connected dots with whiskers) for normal subjects in three age ranges, according to Cook et al.[19]. Open (MEP) and closed (MIP) circles show values obtained in our patients.

In the Group C, greater thoracic restriction (i.e., low TLC) and greater respiratory muscle weakness (i.e., low MIP and MEP) were found. It is possible to observe that 3/15 patients from Group A and 9/9 from Group C could not reach the predicted TLC to perform the MEP. While 10/15 patients from Group A and 7/9 from Group C did not reach the RV predicted to perform MIP. Moreover, 91% (4/43) of MIP and MEP values were below standard deviation (whiskers) of the reference value for the lung volumes at which the manoeuvre was performed.

When MIP was compared to predicted values at RV, MIP in % predicted had a median of 53, 43 and 31% for Group A, B and C respectively (Fig. 2 upper panel). Compared to % predicted for the reached lung volume (the true RV for each patient), a median of 75, 52 and 34% was obtained in those Groups. There was a significant statistical difference for Group A ($p < 0.025$).

Conversely, when MEP was compared to predicted values at TLC, MEP in % predicted had a median of 42, 33 and 18% for Group A, B and C respectively (Fig. 2 lower panel). Compared to the percentage predicted for the reached lung volume, (the true TLC for each patient) a median of 44; 49 and 28% was obtained in those Groups. There was a significant statistical difference for Groups B ($p < 0.031$) and C ($p < 0.008$).

TABLE 1.– *Anthropometric and clinical characteristics of 43 subjects with Duchenne muscular dystrophy*

Group	Group A	Group B	Group C	Total
Variables	7 to 11 years	12 to 16 years	17 to 20 years	7 to 20 years
n	15	19	9	43
Age (years)	9 (8-10)	14 (13-16)	18 (18-19)	13 (10-16)
Arm span (cm)	131 (123-138)	152 (143-170)	172 (160-174)	145 (133-162)
Weight (kg)	30.0 (28.7-35.5)	42.0 (34.4-50.0)	54.0 (43.0-60.0)	38.0 (31.5-50.5)
BMI (kg/m^2)	18.8 (16.5-19.9)	17.0 (14.7-21.0)	19.8 (14.5-21.7)	18.3 (15.1-20.7)
MFC	2 (2-4)	9 (7.5-9)	9 (8.2-9.2)	8 (3-9)
FVC (L)	1.59 (1.41-1.81)	1.61 (1.13-1.96)	1.24 (0.92-1.76)	1.58 (1.19-1.89)
FVC (%)	85.1 (74.6-93.2)	49.8 (31.2-55.8)	25.6 (20.5-35.2)	54.7 (33-80.8)
FEV_1 (L)	1.55 (1.34-1.76)	1.61 (1.02-1.91)	1.24 (0.89-1.76)	1.41 (1.15-1.84)
FEV_1 (%)	93.3 (85.2-101.3)	55.6 (29.6-61.6)	30 (23.2-41.6)	60.8 (32.9-90.2)
FEV_1/FVC	96.9 (91-99.3)	97.5 (93.8-100)	97.3 (93.2-100)	97.3 (93-100)
MIP (cmH_2O)	-63.9 (-67.2 to -50.5)	-57.0 (-64.9 to -43.3)	-42.0 (-53.0 to -40.0)	-53.0 (-65.5 to -41.8)
MIP (%)[17]	53.2 (42.1-56.0)	43.2 (32.8-49.1)	30.8 (30.1-36.8)	42.5 (33.3-50.8)
MEP (cmH_2O)	71.0 (60.0-82.6)	56.0 (41.0-75.8)	41.0 (33.0-52.0)	58.0 (41.5-74.8)
MEP (%)[17]	42.0 (35.5-48.9)	33.5 (24.5-45.4)	18.4 (15.9-19.8)	33.7 (23.9-44.5)
TLC (L)	2.33 (2.00-2.74)	2.60 (2.07-3.52)	2.66 (2.22-2.97)	2.48 (2.05-2.95)
TLC (%)	99.0 (89.0-108.0)	76.0 (53.5-85.5)	40.0 (34.0-46.0)	78.0 (49.0-94.0)
RV (L)	0.59 (0.49-0.77)	1.0 (0.83-1.31)	1.17 (1.07-1.54)	0.88 (0.61-1.16)
RV (%)	24.0 (20.5-31.7)	28.2 (24.4-31.2)	20.2 (16.0-22.9)	27.0 (19.7-30.1)
RV/TLC	27.3 (21.6-31.1)	40.4 (33.9-46.1)	50.3 (47.1-53.2)	35.3 (28.1-47.7)

BMI: body mass index; MFC: motor functional capacity[12]; FVC: forced vital capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; RV: residual volume; TLC: total lung capacity

Values expressed as median (interquartile range)

Fig. 1.– Charts represent the lung volume (in % of TLC) and maximal static pressures at the mouth. Lung volumes (Y-axis) are expressed as a percent of predicted values. Maximal static pressures (X-axis) are expressed in cmH_2O. The curved lines to the left and right represent the mean values ± SD for maximal static pressures for each lung volume[19]. Panel Charts: Group A: age 7 to 11 years; Group B: age 12 to 16 years; and Group C: age 17 to 20 years. It is evident that many subjects with DMD were unable to reach their expected RV and TLC. Most of the MIP and MEP values were outside the expected value for each lung volume. Points (a), (b), and (c) in panel B denote an example from a patient: (a) is the predicted value, taken from normal subjects capable of reaching TLC = 167 cmH_2O; (b) is the MEP value obtained from the patient = 64 cmH_2O at 50% predicted TLC; (c) is the predicted value at the same volume reached by the patient in point (b) = 128 cmH_2O at 50% TLC. If (b) is compared against (a), the percent predicted is 38.3%. If it is compared against (c), the percent predicted is 50%

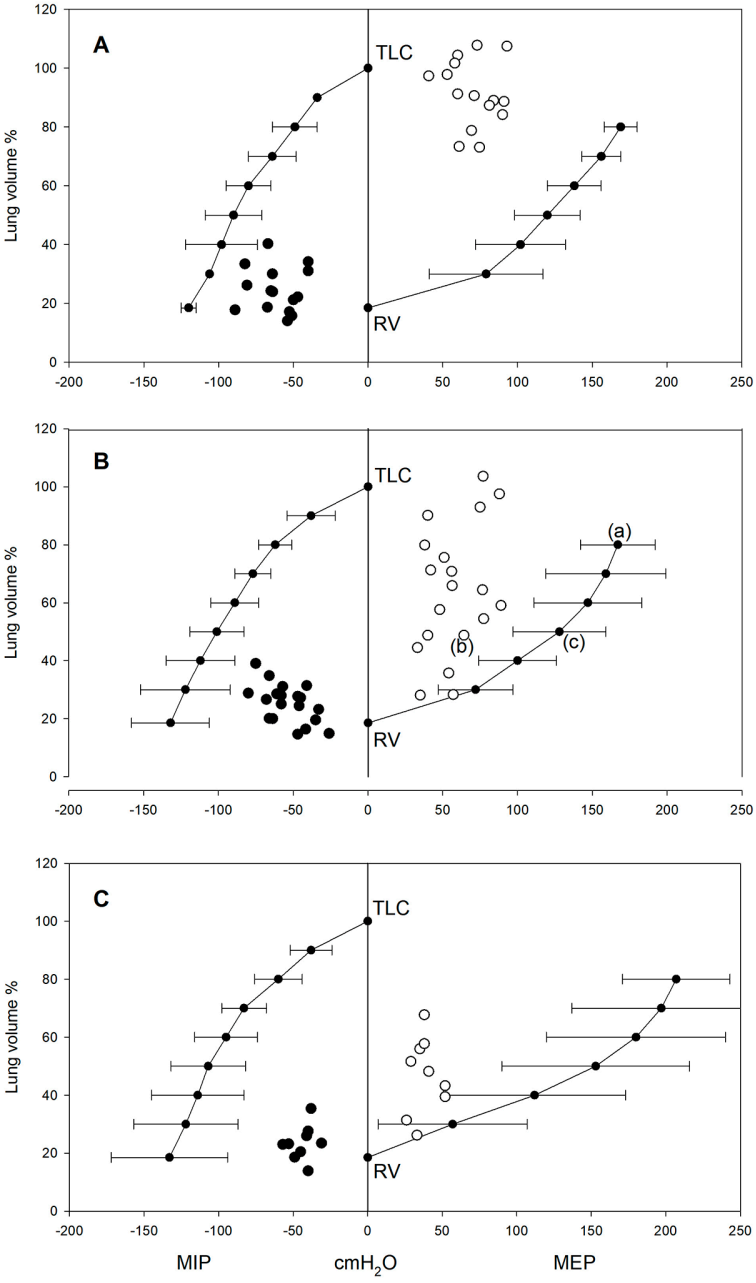
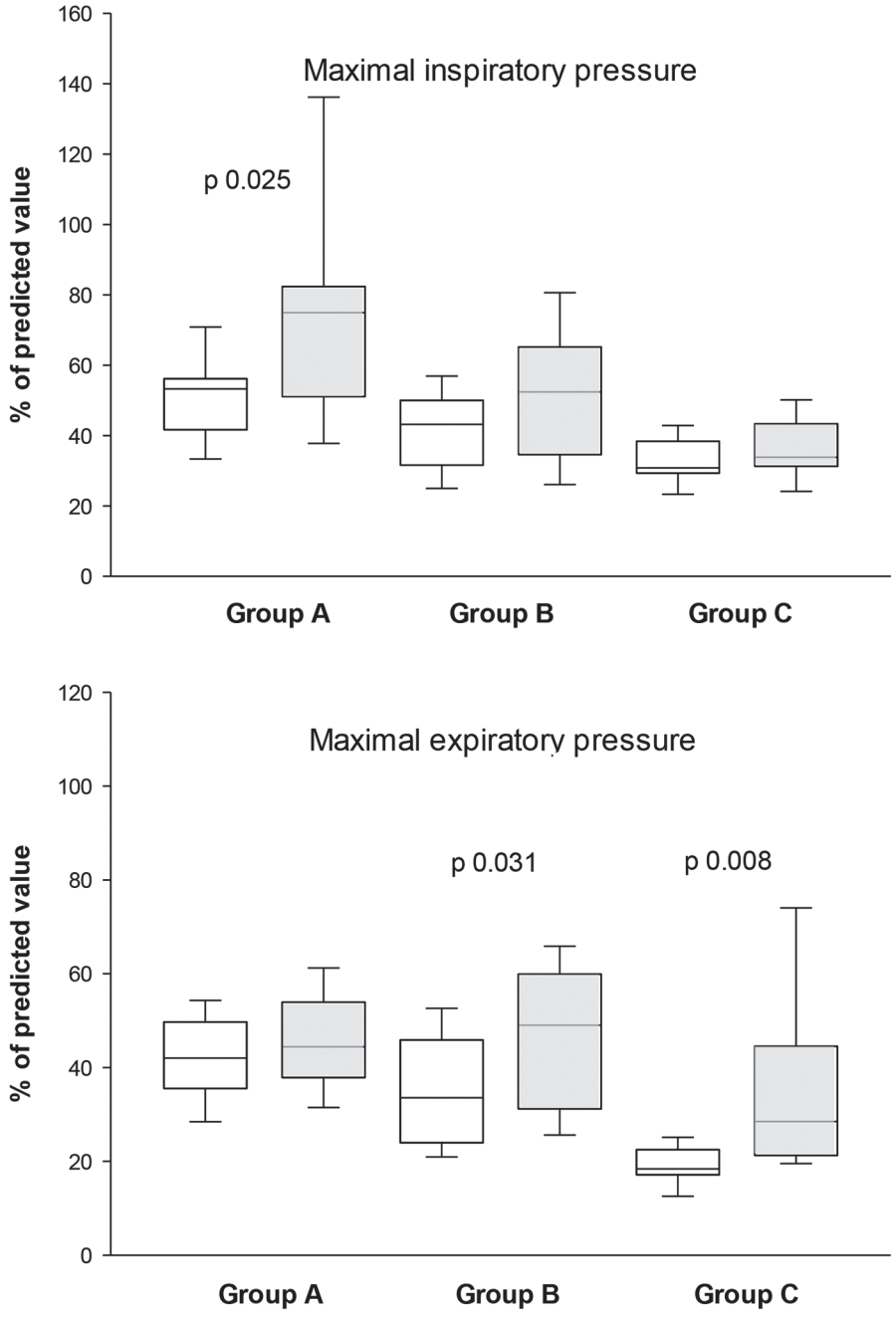


Fig. 2.– Comparison of percentages of the predicted value (white boxes) when predicted RV and TLC are considered and when corrected to the real RV and TLC of each patient (grey boxes)



Discussion

This study provides data for an alternative interpretation of force generation in subjects with DMD beyond muscle weakness. We found that the intrinsic weakness of respiratory muscles and mechanical disadvantage lead to inadequate maximal static pressure generation. Data expressed in percent of predicted values should be interpreted cautiously.

Measuring the maximum static pressures (MIP and MEP) is a simple way to gauge inspiratory and expiratory muscle strength. However, interpretation of low

results, such as in neuromuscular diseases, can be problematic[20].

In normal subjects, maximal static pressures in the mouth are not strictly indicative of the force developed by the respiratory muscles. The passive elastic recoil pressure of the respiratory system (lung and chest wall) counts for the pressure generated by respiratory muscles[20]. Only at functional residual capacity (FRC), when the forces of the collapsing lung and the expanding force of the rib cage are equal (and opposites), the static pressure measured in the mouth is virtually equivalent to the force developed only by the respiratory muscles. However, at residual volume (RV), where MIP is usually measured, the passive elastic recoil pressure of the respiratory system may be as much as 30 cmH_2O and thus makes a significant contribution to MIP of up to 30%. Similarly, since MEP is measured at TLC, the respiratory system recoil pressure can be up to 40 cm H_2O[20]. Then, as FRC is difficult to establish, and MIP and MEP are maximal forces, they are measured after complete exhalation at or near RV and full inhalation at or near TLC respectively[21, 22]. It is usual practice to report MIP and MEP values in % predicted of reference values obtained with this technique[17]. Our results suggest that using this comparator may lead to overestimation of respiratory muscle weakness.

When providing a trend of lung function data over multiple visits, the serial display of absolute values is recommended[21], especially in adults. Our results provide additional data supporting the use of absolute values instead of predicted ones.

The implications of these results on cough assistance manoeuvres should be also discussed. Predicted values for maximal static pressures at the mouth are established from measuring normal subjects, who can satisfactorily reach RV and TLC [for example, point (a) in Fig. 1B]. Absolute values obtained during testing are usually compared to them. But because of respiratory muscle weakness, and in some cases thoracic deformities, most of our DMD subjects failed to reach RV and TLC. As can be seen in the example shown in Figure 1, expected MEP value for that patient is 167 cmH_2O [point (a) in panel B]. As the patient had a MEP value of 64 cmH_2O [point (b)], it is considered to be 38.3% of predicted (obtained value/predictive value $\times$ 100 = 64 cmH_2O/167 cmH_2O x 100 = 38.3%). But the patient reached only 50% of TLC [point (c)], lowering the contribution of elastic recoil to the MEP value obtained. Then, a new percent predicted can be calculated as 50% (obtained value/predicted value at that volume $\times$ 100 = 64 cmH_2O/128 cmH_2O $\times$ 100 = 50%). As such, percent predicted values of maximal static pressures lack strength in clinical interpretation of MIP and MEP.

The difference between both predicted percentages (Fig. 2) can be attributed to pressure generating capacity of elastic recoil of the thoracopulmonary system. From a practical point of view, this can be appreciated when air-staking manoeuvres are performed, as they inflate the lungs, increasing elastic recoil and improving cough strength and airway clearance[23,24]. The extent to which MEP and peak expiratory flow values are affected by changes in lung volume with air application warrants further investigation.

There were limitations to our study, the first of which was that the data were retrospectively collected. Respiratory function in patients with DMD is monitored by routine measurement of FVC, MIP, and MEP[9]. The limitations and the difficulties associated with these volitional measures were considered[8,9]. Some subjects find it difficult to perform truly maximal efforts due to a lack of motivation or genuine problem with the manoeuvre.

As could be expected from the natural evolution of the disease, reached volume was lower in the older patients (Fig. 1C). This is probably an expression of the large contribution of thoracic rib cage deformity to the mouth pressures generation than from weakening of the respiratory muscles. Although our study includes only DMD patients, its findings could be extrapolated to other neuromuscular diseases, especially when progressive thoracic deformity is present, such as spinal muscular atrophy, limb-girdle muscular dystrophy and others.

In conclusion, maximal static pressures should be interpreted cautiously as they overestimate respiratory muscle weakness when compared to predicted values obtained at TLC and RV. Our results provide additional data supporting absolute values use rather than predicted values.

Conflict of interest: None to declare

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