Muscle Impairment in Neuromuscular Disease Using an Expiratory/Inspiratory Ratio

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BACKGROUND: Neuromuscular diseases (NMDs) lead to different weakness patterns, and most patients with NMDs develop respiratory failure. Inspiratory and expiratory muscle strength can be measured by maximum static inspiratory pressure (P_{Imax}) and maximum static expiratory pressure (P_{Emax}), and the relationship between them has not been well described in healthy subjects and subjects with NMDs. Our aim was to assess expiratory/inspiratory muscle strength in NMDs and healthy subjects and calculate P_{Emax}/P_{Imax} ratio for these groups. METHODS: Seventy (35 males) subjects with NMDs (amyotrophic lateral sclerosis, myasthenia gravis, and myotonic dystrophy), and 93 (47 males) healthy individuals 20–80 y of age were evaluated for anthropometry, pulmonary function, P_{Imax}, and P_{Emax}, respectively. RESULTS: Healthy individuals showed greater values for P_{Imax} and P_{Emax} when compared with subjects with NMDs. P_{Emax}/P_{Imax} ratio for healthy subjects was 1.31 ± 0.26, and $P_{Emax}\%/P_{Imax}\%$ was 1.04 ± 0.05; for subjects with NMDs, P_{Emax}/P_{Imax} ratio was 1.45 ± 0.65, and $P_{Emax}\%/P_{Imax}\%$ ratio was 1.42 ± 0.67. We found that $P_{Emax}\%/P_{Imax}\%$ for myotonic dystrophy was 0.93 ± 0.24, for myasthenia gravis 1.94 ± 0.6, and for amyotrophic lateral sclerosis 1.33 ± 0.62 when we analyzed them separately. All healthy individuals showed higher P_{Emax} compared with P_{Imax}. For subjects with NMDs, the impairment of P_{Emax} and P_{Imax} is different among the 3 pathologies studied ($P < .001$). CONCLUSIONS: Healthy individuals and subjects with NMDs showed higher P_{Emax} in comparison to P_{Imax} regarding the P_{Emax}/P_{Imax} ratio. Based on the ratio, it is possible to state that NMDs show different patterns of respiratory muscle strength loss. P_{Emax}/P_{Imax} ratio is a useful parameter to assess the impairment of respiratory muscles in a patient and to customize rehabilitation and treatment. *Key words: respiratory muscle strength; respiratory muscle imbalance; neuromuscular diseases; respiratory therapy; P_{Emax}/P_{Imax} ratio.*
[Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Neuromuscular diseases (NMDs) such as amyotrophic lateral sclerosis (ALS), myasthenia gravis (MG), and myo-

tonic dystrophy (MD) show reductions of maximum static inspiratory pressure (P_{Imax}) and maximum static expira-

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tory pressure (P_{Emax}) as well as an imbalance of inspiratory versus expiratory muscles. NMDs lead to weakness of either inspiratory or expiratory muscles, or both, and in advanced stages, most patients with NMDs develop respiratory failure.[1]

Measurements of P_{Imax} and P_{Emax} at the mouth were proposed by Black and Hyatt[2] in the late 60s as a noninvasive and simple method to determine inspiratory and expiratory muscle strength.[3] Nowadays, this technique is widely used for clinical assessment, and a great number of authors have reported data regarding patients affected by different neurologic diseases.[4-6]

Inspiratory and expiratory muscles are both essential not only to allow ventilation, but also to preserve upper airway patency by an efficient cough mechanism that needs both inspiratory and expiratory muscle strength.[4] In patients with NMDs, the reduction of inspiratory and/or expiratory muscle strength is thus related to ineffective alveolar ventilation and difficult airway clearance, which lead to increased risk of developing atelectasis, pneumonia and chronic respiratory insufficiency.[7-9]

Therefore, the assessment of absolute and relative inspiratory and expiratory muscle impairment is of high clinical relevance. Veale et al[6] found a significant difference between P_{Imax} and P_{Emax} values in subjects with NMDs, namely facio-scapulo humoral dystrophy, limb girdle dystrophy, spinal muscular atrophy, mitochondrial myopathy, and polymyositis.

It is well known that, in the clinical course of ALS, respiratory muscle dysfunction is present in both inspiratory and expiratory muscles and shows a fast progression, whereas, in MD and MG, the respiratory muscle weakness shows a slower clinical course. Nevertheless, the relationship between inspiratory and expiratory muscle strength in NMDs and healthy subjects is unclear[10] or has, at least, not been established. Our aim was to assess expiratory/inspiratory muscle strength in NMDs and healthy subjects and to calculate P_{Emax}/P_{Imax} ratios for all groups as well as to compare these values between study groups. Based on previous findings, we hypothesized that all subjects with NMDs would show respiratory weakness, but with different inspiratory/expiratory weakness patterns according to the disease's characteristics.

Methods

Subjects

Two samples were invited to participate in the study, subjects with neuromuscular disease and healthy individuals, as a control group. Both were recruited for the study from February 2008 to February 2010. All subjects were recruited during routine follow-up visits at the Onofre Lopes University Hospital (Natal, Rio Grande do Norte, Brazil).

QUICK LOOK

Current knowledge

Neuromuscular diseases lead to different weakness patterns, and many patients go on to develop respiratory failure. Inspiratory and expiratory muscle strength are commonly measured by maximum static inspiratory pressure (P_{Imax}) and maximum static expiratory pressure (P_{Emax}).

What this paper contributes to our knowledge

Healthy individuals and subjects with neuromuscular diseases showed higher P_{Emax} in comparison to P_{Imax}. Based on the P_{Imax}/P_{Emax} ratio, it was possible to demonstrate that neuromuscular diseases show different patterns of respiratory muscle strength loss. P_{Imax}/P_{Emax} ratio was a useful parameter to assess the impairment of respiratory muscles and to customize rehabilitation and treatment.

The study was performed at PneumoCardioVascular and Respiratory Muscle Performance Laboratory, Physical Therapy Department/Universidade Federal do Rio Grande do Norte. We included subjects diagnosed by the same neurologist (METD), based on clinical history and clinical stability (ie, without any exacerbation and not hospitalized) for at least 6 months before data collection. Cardiac or respiratory alterations were considered criteria for exclusion. Healthy subjects were recruited in the academic community (students, professors, and professionals) by public announcements. Volunteers with a history of other respiratory or heart diseases or neurological conditions that could influence the results, as well as those using any medication, were excluded. All participants gave written consent, and the study was approved by the hospital ethics committee (protocol 151/07). All procedures were conducted in accordance with the ethical standards of the Helsinki declaration.[11]

Study Design

After the physiotherapist gave a brief explanation on the purposes of the study and the adopted protocol, individuals submitted to an interview, anthropometric evaluation, spirometry, and muscle strength testing. Weight and height were assessed by Welmy scale R-110 (Welmy, Santa Bárbara d'Oeste, Brazil) and body mass index (BMI) was successively calculated. Spirometry and respiratory muscle strength were assessed in all subjects at the same day by the same experienced technician, in a single session. A resting period of 3 min was given to the subject between

the tests. Resting time was increased if necessary (eg, at subject's request). Spirometry and maximal inspiratory and expiratory pressure were performed with the subject in a seated position.

Spirometry

Technical procedure, acceptability, and reproducibility criteria, as well as standardizations for measures, were in accordance with the Brazilian Society of Tisiology and Pneumology.[12] Subjects were instructed about the procedures to be performed during the spirometry assessment. The spirometer was calibrated before the test, using a 3-L syringe, according to ambient temperature conditions. Participants were positioned sitting on a chair with feet supported and trunk flexion of 90°, with hands on the thighs without additional support. A nose clip was used, and subjects were instructed to take 3 slow breaths at tidal volume level through the mouth. On the fourth breath, they were required to perform a maximal inspiration to total lung capacity. Then, immediately after positioning the spirometer in the mouth, through a tubular stiff paper mouthpiece, participants were instructed to conduct a full and fast expiration (FVC maneuver) under vigorous verbal encouragement by the examiner. For the implementation of the FVC maneuver, participants were instructed to place the mouthpiece between the teeth, on the tongue, and keep it firmly with the lips placed around it, to prevent air leakage. Furthermore, anterior trunk flexion was not allowed during the procedure. A minimum of 3 and a maximum of 8 tests were conducted, with a 1-min interval between them. A Datospir 120 spirometer (Sibelmed, Barcelona, Spain) was used to measure FEV_1 and FVC. Three reproducible maneuvers were performed, and the best curve was considered for the study. Results were expressed in both absolute and as percent-of-predicted values.[13]

Respiratory Muscle Strength

Respiratory muscle strength was assessed based on maximal respiratory pressure (P_{Imax} and P_{Emax}) procedures as originally described by Black and Hyatt.[2] Pressures were measured with the subjects in the same position adopted during spirometry, with the nostrils occluded with a nose clip and by using a paper mouthpiece. P_{Imax} and P_{Emax} were measured using a MicroRPM digital manometer (Micro Medical, Rochester, United Kingdom), respectively, at residual volume and total lung capacity. A total of 5–8 maneuvers were performed until 2 maximal values were reproducible (in accordance with the reproducibility and acceptability criteria standardized by the Brazilian Society of Pneumology and Tisiology).[12] We considered the greatest pressure value obtained, with variation less than 10% among the 3 highest maneuvers. P_{Imax} and P_{Emax} were

expressed both in absolute and in percent-of-predicted values, using reference values obtained for the Brazilian population.[14]

Statistical Analysis

Participants were characterized using descriptive statistics, obtaining the means ± SD of age and BMI. The Shapiro-Wilk test was used to verify data normally. Unpaired t test was applied to compare subjects with NMDs and healthy subjects. P_{Emax}/P_{Imax} ratio was established through a single linear regression in healthy individuals and subjects with NMDs. Spirometric variables and respiratory pressures between the subjects with 3 types of NMDs and healthy subjects were calculated by one-way analysis of variance with Bonferroni post hoc test. For statistical analysis, Prism 5 (GraphPad Software, San Diego, California) software was used. Significance level was set at $P < .05$ with 2-tailed approach.

Results

Baseline Characteristics

The study included 70 subjects (35 males) with NMDs and 93 (47 males) healthy individuals 20–80 y of age. Subjects with NMDs were diagnosed as follows: MD (36%), 18–76 y of age; MG (39%), 33–80 y of age; and ALS (26%), 39–76 y of age. No subject was wheelchair-dependent at the moment of respiratory variable collection; however, 7 subjects with ALS were receiving nocturnal noninvasive ventilation. Regarding BMI, healthy individuals and subjects with MD and ALS were considered to be optimal weight, whereas subjects with MG were classified as overweight according to World Health Organization standards.[15]

The subjects' anthropometric characteristics and spirometric data are presented in Table 1. Healthy individuals and subjects with NMDs were similar in gender and BMI, but age was significantly different ($P < .001$). The 3 groups of subjects with NMDs were different in terms of gender, age, and BMI ($P < .001$). FVC, FVC (% predicted), FEV_1, FEV_1 (% predicted), and FEV_1/FVC, were significantly different between healthy individuals and subjects with NMDs ($P < .001$), as well as between the 3 groups of subjects with NMDs ($P < .001$) (Table 1).

P_{Emax} and P_{Imax} Ratio in Healthy Individuals and in Neuromuscular Subjects

Table 2 reports P_{Emax} (absolute and % predicted), P_{Imax} (absolute and % predicted), P_{Emax}/P_{Imax} ratio, and percent-of-predicted P_{Emax}/P_{Imax} ratio in all the considered groups. All parameters (both absolute values and ratios)

Table 1.   Demographic and Anthropometric Characteristics and Lung Function Values

	Healthy Subjects (n = 93)	NMDs (n = 70)	MD (n = 25)	MG (n = 27)	ALS (n = 18)
Demographic and anthropometric characteristics					
Age (y)	43.6 ± 16.3	53.1 ± 17.5*	39 ± 15.5	64.5 ± 13*†§	55.3 ± 11.9*†§
Sex	47 M, 46 F	35 M, 35 F	15 M, 10 F	13 M, 14 F	10 M, 8 F
BMI (kg/m²)	25.1 ± 2.8	25.2 ± 5.4	22.9 ± 5	28.2 ± 3.9*†	23.7 ± 5.6†§
Lung function					
FVC (L)	3.9 ± 1.04	2.8 ± 1.04*	2.9 ± 0.97*	2.8 ± 0.98*	2.5 ± 1.28*
FVC%	94.4 ± 10	76.6 ± 20*	76.8 ± 15*	79.8 ± 14.5*	71 ± 29*
FEV_1 (L)	3.3 ± 0.8	2.2 ± 0.88*	2.4 ± 0.8*	2.1 ± 0.82*	1.9 ± 0.98*
FEV_1 (%)	97.8 ± 12	76.6 ± 23*	75.1 ± 18*	80.5 ± 18*	72.5 ± 32*
FEV_1/FVC	0.84 ± 0.06	0.78 ± 0.01*	0.82 ± 0.1	0.72 ± 0.8*†	0.81 ± 0.13§

Table shows mean ± SD of spirometric parameters of groups: t test between healthy subjects and all subjects with NMDs. One-way analysis of variance with Bonferroni post hoc test was conducted among healthy individuals and the 3 groups of subjects with NMDs separately. $P < .01$ for all significance.
* vs healthy subjects.
† vs subjects with MD.
‡ vs subjects with ALS.
§ vs subjects with MG.
NMD = neuromuscular disease
MD = myotonic dystrophy
MG = myasthenia gravis
ALS = amyotrophic lateral sclerosis
M = male
F = female
BMI = body mass index

Table 2   Maximal Inspiratory Pressure, Maximal Expiratory Pressure, and Maximal Expiratory/Inspiratory Pressure Ratio Values for Healthy Individuals and Neuromuscular Subjects

	Healthy Subjects (n = 93)	NMDs (n = 70)	MD (n = 25)	MG (n = 27)	ALS (n = 18)
P_{Emax} (cm H_2O)	133 ± 33	83 ± 38*	69 ± 20*	109 ± 37*	63 ± 37*
P_{Emax} (% pred)	122 ± 21.3	84.6 ± 41.8*	62 ± 21*	122.5 ± 35†	60 ± 29*‡
P_{Imax} (cm H_2O)	102 ± 26	62 ± 27*	75 ± 30*	58.3 ± 20*	50 ± 26*†
P_{Imax} (% pred)	97 ± 16.1	63 ± 23.2*	68.6 ± 23.6*	65.5 ± 18.1*	51 ± 26.2*
P_{Emax}/P_{Imax}	1.31 ± 0.26	1.45 ± 0.65	0.96 ± 0.24*	1.96 ± 0.56*†	1.37 ± 0.65†‡
P_{Emax}/P_{Imax} (% pred)	1.04 ± 0.05	1.42 ± 0.67*	0.93 ± 0.24*	1.94 ± 0.60*†	1.33 ± 0.62*†‡

Values are mean ± SD of respiratory muscular strength, determined by t test between healthy subjects and all subjects with NMDs. One-way analysis of variance with Bonferroni post hoc test was conducted among healthy individuals and the 3 groups of NMDs separately.
* vs healthy subjects.
† vs subjects with MD.
‡ vs subjects with MG.
P_{Emax} = maximal expiratory pressure
% pred = percent of predicted
P_{Imax} = maximal inspiratory pressure
NMD = neuromuscular disease
MD = myotonic dystrophy
MG = myasthenia gravis
ALS = amyotrophic lateral sclerosis

were significantly different between healthy subjects and subjects with NMDs. P_{Emax}/P_{Imax} ratios were different in the different NMD groups.

Individual values of P_{Emax}/P_{Imax}, both absolute and percent-of-predicted values, are shown in Figure 1. In healthy subjects, P_{Emax}/P_{Imax} (ratio between absolute values) was, on average, greater than 1. In subjects with MD and MG, this ratio was lower and higher than for healthy subjects, respectively. In subjects with ALS, although the average value was similar to healthy subjects, the variability was extremely large. When considering P_{Emax}/P_{Imax} (ratio between predicted values), this was, as expected, on average very close to 1 in healthy subjects with a very low spread. In the 3 considered NMDs, the variability of this
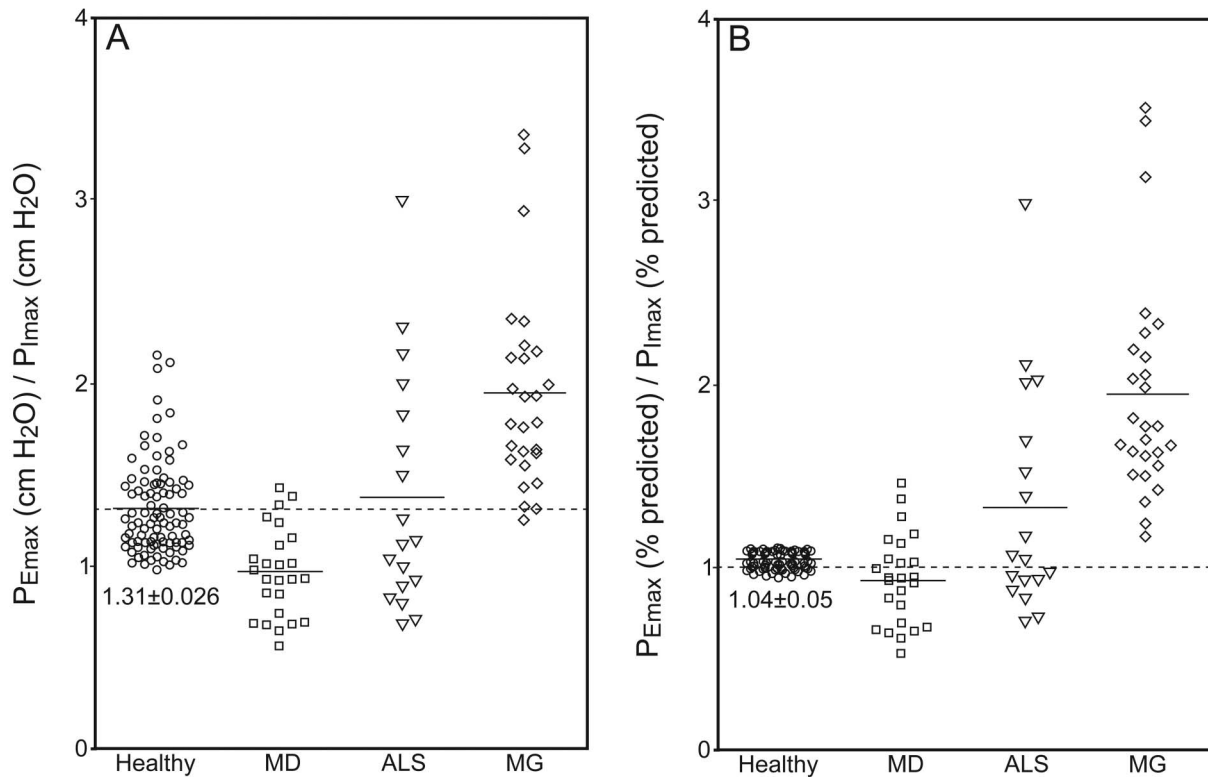
Fig. 1. P_{Emax}/P_{Imax} ratio for healthy individuals and subjects with NMDs. The distribution of absolute (A) and percent-of-predicted (B) values for each pathology is shown. ALS = amyotrophic lateral sclerosis; MG = myasthenia gravis; MD = myotonic dystrophy; P_{Emax} = maximum static expiratory pressure; P_{Imax} = maximum static inspiratory pressure. Analysis of variance with Bonferroni post hoc test was applied to identify differences among healthy subjects in relation to each group of NMD. $P < .001$ was considered significant. Dotted horizontal lines represent the overall mean; solid horizontal lines denote the mean for each group.

ratio was generally high and tended to increase passing from MD to ALS to MG.

As shown in Figure 2 (upper left panel), all healthy individuals were above the identity line ($P_{Emax} = P_{Imax}$), showing higher P_{Emax} compared with P_{Imax}. Conversely, a significant number of subjects with NMDs were below the dotted line, meaning that the impairment of P_{Emax} and P_{Imax} followed a complex pattern. When analyzing the relationship between P_{Emax}/P_{Imax} and age (Fig. 2, bottom panels), it was found that, in healthy subjects, the ratio was invariant with age, whereas, in NMDs, again, it followed a more complex pattern. In older subjects, variability of P_{Emax}/P_{Imax} was greater than in younger subjects. When the same relationship was analyzed in the different NMDs (Fig. 3), we found that only in MD, but not in MG and ALS, a significant progressive increase of P_{Emax}/P_{Imax} ratio with age was present (MD: $r^2 = 0.27$, $P = .008$; MG: $r^2 = 0.07$, $P = .18$; ALS: $r^2 = 0.18$, $P = .08$).

Discussion

NMDs are progressive conditions leading to respiratory failure and severe disability. Therefore, a close clinical follow-up and a systematic evaluation of respiratory muscles and lung function are essential.[16] In the present study, we introduce the P_{Emax}/P_{Imax} (ratio between both absolute and percent of predicted values) as a simple way to describe the relative impairment of inspiratory versus expiratory muscles in NMDs. The main findings were that P_{Emax}/P_{Imax} is lower than normal in MD, higher than normal in MG, and highly variable in ALS. This means that, in MD, expiratory muscles are relatively more impaired than inspiratory muscles, vice versa in MG, whereas, in ALS, a more complex and variable situation is present.

Our results regarding subjects with MD are in agreement with those of Veale et al,[6] who compared respiratory pattern during sleep and wakefulness in healthy subjects and subjects with MD and other NMDs. These authors found that, despite a similar degree of respiratory muscle weakness in the 2 groups of subjects, those with MD showed lower P_{Emax}, suggesting more impairment of expiratory muscles, presumably abdominal ones.

Regarding the subjects from our MG group, the relationship P_{Emax}/P_{Imax} was the highest compared with the other considered NMDs. In our MG group, 17 subjects (55%) showed P_{Emax} values similar to those of healthy
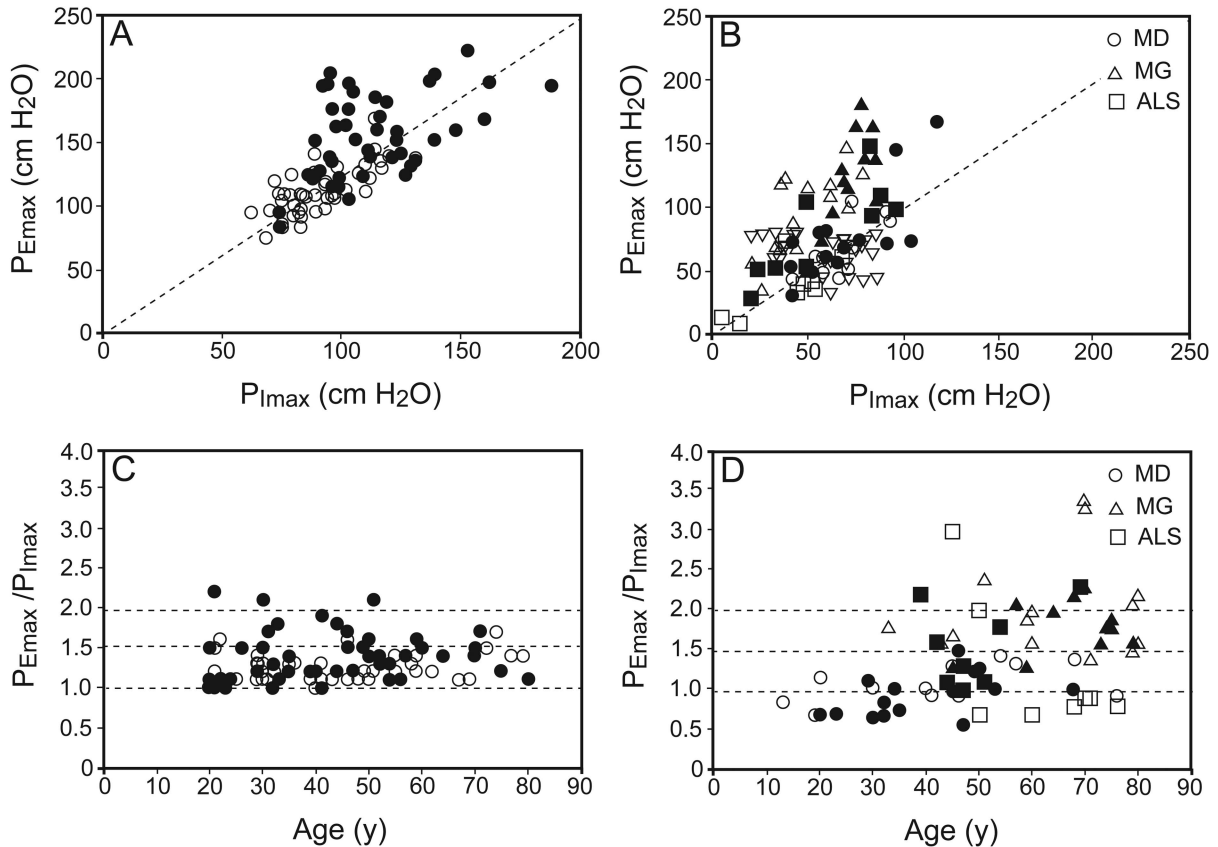
Fig. 2. Relationship between P_{Emax} and P_{Imax} for healthy individuals (A) and subjects with neuromuscular diseases (NMDs) among the pathologies (B). Also shown is the P_{Emax}/P_{Imax} ratio relationship to age in healthy subjects (C) and subjects with NMDs (D). Open shapes are females, and closed shapes are males. ALS = amyotrophic lateral sclerosis; MG = myasthenia gravis; MD = myotonic dystrophy. In C, the horizontal lines represent the majority concentration of healthy subjects (1.5 ± 0.5) They are repeated in D to compare the distribution of NMD subjects.
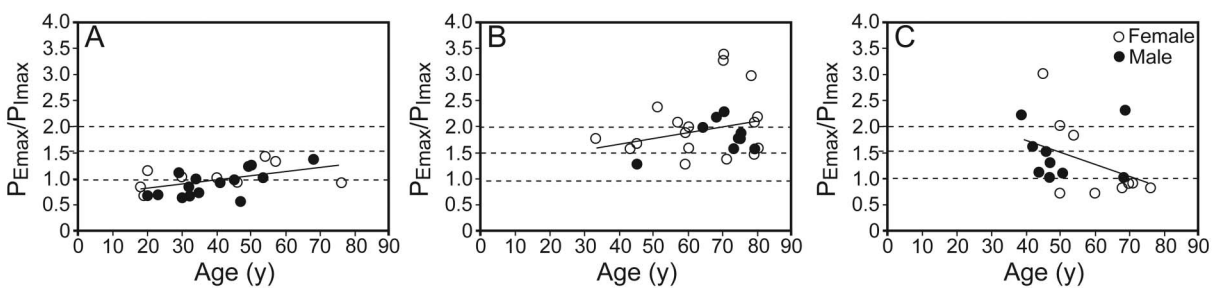

Fig. 3. P_{Emax} minus P_{Imax} versus age for myotonic dystrophy (A), myasthenia gravis (B), and amyotrophic lateral sclerosis (C). Single linear regression was used to identify a P_{Emax} minus P_{Imax} versus age pattern ($p < .001$). Open shapes are females, and closed shapes are males. Horizontal lines indicate the majority concentration in healthy subjects (1.5 ± 0.5) as a comparison.

subjects and 27 subjects (100%) lower P_{Imax} values, so determining high values of P_{Emax}/P_{Imax}. Our results are apparently in partial disagreement with those of Weiner et al[17] and Keenan et al,[18] who studied subjects with severe and moderate generalized MG, and found that both P_{Emax} and P_{Imax} were lower than normal. However, our group of MG subjects included those with only mild/moderate, and not severe, generalized MG.

Our ALS subjects had, on average, a P_{Emax}/P_{Imax} ratio similar to healthy subjects. The variability, however, was extremely high, presumably due to disease severity and/or disease progression. Several previous studies tried to es-

tablish a relationship between the degree of respiratory muscle weakness and distribution of weakness (diaphragmatic vs overall muscle weakness) and lung volumes. Qureshi et al[5] investigated risk factors and predictors of disease progression in 95 subjects with ALS and 106 healthy subjects over 12 months. They observed normal total lung capacity, elevated residual volume, reduced FVC, and diminished respiratory muscle strength (both inspiratory and expiratory), with a greater decline in P_{Emax} than in P_{Imax}. The study showed that a marked reduction in P_{Emax} determines increased residual volume, and, in more general terms, a lower efficiency in the use of expiratory muscles. Park et al[4] studied 45 ALS subjects, and also found that both P_{Emax} and P_{Imax} were markedly decreased, in addition to a lower P_{Emax} (% predicted)/P_{Imax} (% predicted) ratio (equal to 0.89), suggesting more impairment in expiratory than inspiratory muscles. These results are in agreement with ours.

A potential limitation of our study is the small sample size of the NMD groups because of the difficulty in the number of subjects available to be part of the study. Furthermore, the different stages/progression of diseases and heterogeneity of sample size, in terms of gender, age, and BMI, as well as including some subjects receiving nocturnal noninvasive mechanical ventilation, are also limitations. However, the main aim of the present study was not to investigate the effect of specific parameters on respiratory muscle strength, but to characterize NMDs in terms of relative impairment of inspiratory and expiratory muscles.

The results add new perspectives in terms of respiratory muscle assessment in subjects with NMDs. The use of P_{Emax}/P_{Imax} ratio, either absolute or percent of predicted, is a simple way to assess the relative impairment of inspiratory versus expiratory muscles and therefore to plan and adjust the treatment. Future studies are needed to further corroborate our findings.

Conclusions

Healthy individuals and subjects with NMDs showed higher P_{Emax} in comparison to P_{Imax} regarding the P_{Emax}/P_{Imax} ratio. Based on the ratio, it is possible to state that NMDs show different patterns of respiratory muscle strength loss. In our study, we found that subjects with MD show a predominant expiratory muscle weakness, and subjects with MG show a predominant inspiratory muscle weakness, whereas, in subjects with ALS, a more complex pattern, presumably dependent on severity/progression of the disease, is present. P_{Emax}/P_{Imax} ratio is a useful parameter to assess the impairment of respiratory muscles in a patient and to customize rehabilitation and treatment.

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