Respiratory Muscle Testing
A Valuable Tool for Children with Neuromuscular Disorders

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Rationale: **Data on respiratory muscle performance in children with neuromuscular disorders are limited.**
Objectives: **The aim of this study was to assess respiratory muscle strength by volitional and nonvolitional tests and to compare these tests with forced vital capacity.**
Methods: **Inspiratory muscle strength was assessed by measuring transdiaphragmatic and esophageal pressures generated during volitional and nonvolitional maneuvers, whereas expiratory muscle strength was assessed by measuring the gastric pressure generated during a cough maneuver. Lung volumes were assessed by measuring forced vital capacity.**
Measurements and Main Results: **Forty-one patients with Duchenne muscular dystrophy (n = 20), spinal amyotrophy (n = 8), and congenital myopathy (n = 13) were included, aged 2 to 18 yr. All the patients were able to perform the sniff and the cough maneuver. Sniff transdiaphragmatic pressure decreased with age in Duchenne patients, whereas it increased with age in patients with spinal amyotrophy and congenital myopathy. Magnetic stimulation of the phrenic nerves was obtained in all patients. Twenty-five (61%) patients were able to perform forced vital capacity. In the three groups of patients, a positive correlation was observed between volitional, assessed by the sniff maneuver, and nonvolitional respiratory muscle tests, assessed by the magnetic stimulation of the phrenic nerves. Also, forced vital capacity correlated with sniff transdiaphragmatic pressure and cough gastric pressure.**
Conclusions: **Volitional respiratory muscle tests correlated with nonvolitional tests and with forced vital capacity. Simple volitional respiratory muscle tests constitute a valuable tool for the assessment of respiratory muscle strength in young patients with neuromuscular disorders.**

Keywords: congenital myopathy; cough maneuver; Duchenne muscular dystrophy; sniff maneuver; spinal amyotrophy

Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy. Despite advances in the treatment of respiratory failure with noninvasive positive-pressure ventilation (NPPV), the life expectancy of affected children has not improved greatly, with death occurring during the second to third decade of life (1). Respiratory insufficiency is the consequence of an imbalance between the respiratory muscle load and capacity. In particular, there is combined inspiratory and expiratory muscle weakness with reduced lung and chest wall compliance, which as well as causing alveolar hypoventilation, reduces cough efficacy (2). The measurement of lung volumes has been demonstrated to be a useful marker of the severity of the respiratory disease in DMD (3, 4), and recent recommendations for the respiratory care of patients with DMD have been reported by the American Thoracic Society (5). Routine evaluation of forced vital capacity (FVC), maximal inspiratory ($P_{I_{max}}$) and expiratory pressures ($P_{E_{max}}$), and peak cough flow (PCF) is suggested early in the course of the disease.

However, noninvasive volitional tests of lung and respiratory muscle function can be misleading. Although measurement of static pressures developed at the mouth during a maximum effort is the simplest method to assess respiratory muscle pressure–generating capacity, these tests require aptitude, cooperation, motivation, and coordination. Accordingly, a low $P_{I_{max}}$ or $P_{E_{max}}$ does not necessarily imply weakness and could result from poor performance of the test. These tests are further criticized because reproducibility does not ensure maximality (6).

More invasive volitional and nonvolitional tests have recently been developed to overcome these problems. One method for the assessment of inspiratory muscle strength is to measure the pressure developed during a maximal sniff, a natural maneuver, which even young children find easy to perform (7, 8). Cough, like a sniff, is also a natural maneuver, and the measurement of cough gastric pressure (Pgas cough) has been shown to be a useful test for the assessment of expiratory muscle strength (9), whereas magnetic stimulation of the phrenic nerves is a test that quantifies diaphragmatic strength in patients unwilling or unable to make voluntary efforts (10, 11). Despite these technological advances, there is a paucity of data in younger patients.

One of the primary goals of the present study was to assess the feasibility of performing detailed respiratory muscle testing in children with DMD and other neuromuscular disorders. Furthermore, we aimed to quantify respiratory muscle strength in this young population and to compare the volitional and nonvolitional techniques of pressure measurements with the standard lung volume measurements to assess the potential advantage and disadvantage of each method. In addition, data would be generated to determine the decline of inspiratory and expiratory pressures with age.

METHODS

Patients

The study was conducted in agreement with the French regulations and received appropriate legal and ethical approval. Patients with DMD were compared with a homogeneous group of patients with spinal amyotrophy and a heterogeneous group of patients with congenital

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myopathy [central core disease (n = 1), merosin deficiency (n = 3), unknown myopathy (n = 9)].

Patients were included if they had been clinically stable for at least 1 mo before the study and were able to perform sniff and cough maneuvers. NPPV was started when necessary according to the international recommendations (12–14).

Pressure and Flow Measurements

Esophageal (Pes) and gastric pressure (Pgas) were measured as previously described (15, 16). Flow was measured using a pneumotachograph (Fleisch No. 2; Lausanne, Switzerland), inserted to the distal end of a mouthpiece. Airway pressure was measured by a pressure transducer (MP 45 model, Validyne ± 2 cm H_2O; Fleisch, Northridge, CA) connected to the mouthpiece.

Breathing Pattern and Respiratory Muscle Output

All data were recorded during a 3-min period after a 5-min period of stabilization. Breathing pattern and minute ventilation ($\dot{V}_E$) were determined from the flow tracing. Tidal volume (V_T) and $\dot{V}_E$ were expressed in ml/kg. Inspiratory work of breathing (WOB) and esophageal (PTPes) and diaphragmatic pressure time product (PTPdi) were computed from the Pes and V_T loops as previously described (16, 17). Dynamic lung compliance (Cdyn) was measured as previously described (18).

All signals were sampled at 128 Hz and passed to a computer (Elonex, Gennevilliers, France). Data were acquired and analyzed using the Biopac system (MP 100; Biopac Systems, Goleta, CA) and Acknowledge software.

Respiratory Muscle Testing

Sniff and cough maneuvers. Patients were asked to perform at least 10 to 20 short, sharp maximal sniffs (19, 20), and the maximum pressure was noted. A mean value of 104 ± 26 cm H_2O in boys and 93 ± 23 cm H_2O in girls is considered normal for the sniff nasal pressure maneuver (7).

For Pgas cough, the peak value of at least five coughs was recorded (9). The maximal Pgas cough value for each patient was included. Mean Pgas cough for normal males is 214 ± 42 cn H_2O, and 165 ± 35 cm H_2O for females (9).

Magnetic Stimulation of the Phrenic Nerves

The unpotentiated twitch Pdi (TwPdi) elicited by phrenic nerve stimulation by the bilateral anterior magnetic phrenic nerve stimulation (BAMPS) technique was used as the nonvolitional method of measuring diaphragm strength (11, 21). At least five phrenic nerve stimulations were obtained in each patient and the mean value was calculated. In healthy adults, mean TwPdi is 27.8 ± 5.5 cm H_2O (11).

Lung Function Testing

All the patients were asked to perform at least three physician-accepted FVC curves, and the curves with the highest FVC were used for the final analysis (22). Results were expressed as a percentage of published values (% pred), with height calculated as the arm span (23, 24).

Arterial oxygen partial pressure (Pa_{O_2}) and arterial carbon dioxide partial pressure (Pa_{CO_2}) were measured from arterialized earlobe capillary blood gases (25). Functional residual capacity (FRC) was measured by the helium dilution technique and was expressed as a percentage of published values (% pred) (26).

Statistical Analysis

Data are presented as mean ± SD. Comparisons between groups were conducted using the Kruskal-Wallis rank sum test. Correlations between sniff, cough, $\dot{V}_E$, FVC, FRC, and age were assessed using simple linear regression analysis. Comparison between the patients treated or not with NPPV was made used a nonparametric Mann-Whitney test. A p value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the Population

Twenty patients with DMD were included in the study (Table 1). The mean age of the patients was 13.3 ± 3.8 yr, with a range of 7 to 18 yr. The mean age at which the patients became wheelchair bound was 12.4 ± 3.6 yr. The three youngest patients, aged between 7 and 8 yr, were still able to walk. Four patients had spinal surgery and a fifth patient had refused surgery. Four patients were being treated with angiotensin converting enzyme (ACE) inhibitors, but none of the patients had received corticosteroids.

The patients with DMD were compared with 8 patients with spinal amyotrophy and 13 patients with congenital myopathy (Table 1). These patients were significantly younger than the patients with DMD and became wheelchair bound at an earlier age.

Breathing Pattern, Lung Function, and Respiratory Muscle Output

Results of breathing pattern, lung function, and respiratory muscle output are presented in Table 2. For the patients with DMD, mean V_T was 7.7 ± 3.5 ml/kg and mean $\dot{V}_E$ was 177 ± 82 ml/kg/min, with a mean ΔPgas/ΔPdi during quiet breathing of −0.16 ± 0.32. Mean Cdyn was 58 ± 35 ml/cm H_2O. Pa_{CO_2} was within the normal limits for all the patients. Fourteen patients were able to perform reproducible FVC maneuvers; FVC could not be obtained in six patients because of the inability to perform reproducible maneuvers due to young age (three patients; age range, 7–8 yr), moderate mental retardation (two patients), and severe respiratory muscle weakness (one patient). Mean FVC of the 14 patients was 41 ± 24% (range, 9–86% pred). There was no correlation observed among any index of respiratory muscle output and age, indices of respiratory muscle strength, lung function, or gas exchange.

Patients with congenital myopathy had a higher respiratory rate than the patients with DMD and spinal amyotrophy. Mean

TABLE 1. CHARACTERISTICS OF THE PATIENTS

	DMD (*n = 20*)	Spinal Amyotrophy (*n = 8*)	Congenital Myopathy (*n = 13*)	p Value
Age, yr	13.3 ± 3.8	10.5 ± 3.7	7.6 ± 3.1	0.001
Weight, kg	45.5 ± 18.7	27.2 ± 11.8	27.2 ± 12.7	0.007
No. patients still walking	4	0	4	
Mean age of wheelchair bound, yr	12 ± 3	5 ± 6	8 ± 3	0.041
Spine surgery, n	4*	0	0	
ACEI treatment, n	4	Not applicable	Not applicable	

Definition of abbreviations: ACEI = angiotensin converting enzyme inhibitor; DMD = Duchenne muscular dystrophy.

Data are presented as mean ± SD. Comparison between the three groups of patients was performed with the Kruskal-Wallis rank sum test.

* One patient refused spinal surgery.

TABLE 2. BREATHING PATTERN, LUNG FUNCTION DATA, AND RESPIRATORY MUSCLE OUTPUT IN PATIENTS

	DMD (*n* = *20*)	Spinal Amyotrophy (*n* = *8*)	Congenital Myopathy (*n* = *13*)	p Value
Breathing pattern				
Tidal volume, ml/kg	7.7 ± 3.5	9.5 ± 3.4	8.8 ± 3.1	NS
Respiratory rate, breaths/min	23 ± 8	20 ± 6	28 ± 8	0.040
Minute ventilation, ml/kg/min	177 ± 82	192 ± 80	267 ± 144	NS
ΔPgas/ΔPdi	−0.16 ± 0.32	0.43 ± 0.22	−0.07 ± 0.34	0.001
Lung function parameters				
Cdyn, ml/cm H_2O	58 ± 35	39 ± 21	45 ± 31	NS
FRC helium, % predicted	87 ± 28	80 ± 18	80 ± 22	NS
FVC, % predicted	41 ± 24	51 ± 34	58 ± 22	NS
	(n = 14)	(n = 4)	(n = 7)	
Pa_{O_2}, mm Hg	91 ± 10	93 ± 6	92 ± 10	NS
Pa_{CO_2}, mm Hg	37 ± 3	41 ± 17	38 ± 3	NS
Respiratory muscle output				
WOB/cycle, J	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	NS
WOB/min, J	4.5 ± 2.3	2.6 ± 0.9	4.3 ± 2.0	NS
WOB/L, J	0.7 ± 0.3	0.6 ± 0.2	0.7 ± 0.3	NS
PTPes/min, cm $H_2O \cdot s \cdot min^{-1}$	172 ± 67	160 ± 63	169 ± 57	NS
PTPdi/min, cm $H_2O \cdot s \cdot min^{-1}$	238 ± 136	364 ± 242	218 ± 154	NS

Definition of abbreviations: Cdyn = dynamic lung compliance; DMD = Duchenne muscular dystrophy; FRC helium = functional residual capacity measured by the helium dilution technique; NS = not significant; ΔPgas/ΔPdi = ratio of gastric pressure swing to transdiaphragmatic pressure swing during spontaneous breathing; PTPdi = diaphragmatic pressure time product; PTPes = esophageal pressure time product; WOB = work of breathing.

Data are presented as mean ± SD. Comparison between the three groups of patients was performed with the Kruskal-Wallis rank sum test.

ΔPgas/ΔPdi during quiet breathing was significantly more positive in patients with spinal amyotrophy than in the two other groups of patients. FVC could not be obtained in the four youngest patients with spinal amyotrophy and in six patients with congenital myopathy due to young age (four patients) and mental retardation (two patients). No significant difference between the three groups was observed for lung function parameters, arterial blood bases, and respiratory muscle output.

Respiratory Muscle Testing

All the patients of the three groups tolerated the insertion of the esophagogastric catheter and were able to perform reproducible sniff and cough maneuvers. In the patients with DMD, the mean values for sniff Pes and sniff Pdi were 39 ± 16 cm H_2O and 37 ± 17 cm H_2O, respectively. Magnetic stimulation of the phrenic nerves demonstrated mean TwPes and TwPdi values of 6 ± 4 cm H_2O and 9 ± 5 cm H_2O, respectively (Table 3). Mean Pgas cough value, as a measure of expiratory muscle function, was 40 ± 25 cm H_2O. Sniff Pes and sniff Pdi correlated positively with Pgas cough ($r = +0.826$, $p < 0.001$, and $r = +0.702$, $p = 0.0012$ for sniff Pes and sniff Pdi, respectively). All patients older than 15 yr had Pgas cough values below 20 cm H_2O. A correlation was observed between volitional and nonvolitional respiratory muscle tests. Indeed, a significant positive correlation was observed between sniff Pdi and TwPdi ($r = +0.890$, $p < 0.0001$). The ΔPgas/ΔPdi ratio, which represents a nonvolitional marker of diaphragm dysfunction, correlated with sniff Pdi ($r = +0.653$, $p = 0.003$) and TwPdi ($r = +0.655$, $p = 0.008$).

Patients with spinal amyotrophy had a higher mean sniff Pdi and sniff Pgas than the two other groups. TwPdi and TwPgas were also greater in these patients, although this difference was not statistically significant. In these patients, no correlation was observed among sniff Pes, sniff Pdi, and Pgas cough, and between sniff Pdi and TwPdi. ΔPgas/ΔPdi correlated with sniff Pdi ($r = -0.714$, $p = 0.047$) but not with TwPdi.

TABLE 3. RESPIRATORY MUSCLE PERFORMANCE

	DMD (*n* = *20*)	Spinal Amyopathy (*n* = *8*)	Congenital Myopathy (*n* = *13*)	p Value
Sniff maneuver, cm H_2O				
Pes	39 ± 16	40 ± 23	44 ± 18	NS
Pdi	37 ± 17	63 ± 20	46 ± 21	0.025
Pgas	−2 ± 8	24 ± 10	1 ± 10	0.001
Cough maneuver, cm H_2O				
Pgas cough	40 ± 25	47 ± 25	60 ± 43	NS
Tw maneuver, cm H_2O				
Pes	6 ± 4	11 ± 6	9 ± 5	NS
Pdi	9 ± 5	16 ± 8	14 ± 8	0.063
Pgas	3 ± 2	8 ± 3	5 ± 4	0.003

Definition of abbreviations: DMD = Duchenne muscular dystrophy; Pes = esophageal pressure; Pdi = transdiaphragmatic pressure; Pgas = gastric pressure; Tw = pressure obtained by the magnetic stimulation of the phrenic nerves.

Data are presented as mean ± SD. Comparison between the three groups of patients was performed with the Kruskal-Wallis rank sum test.

Patients with congenital myopathy presented an intermediate pattern. Sniff Pes and sniff Pdi correlated positively with Pgas cough ($r = +0.695$, $p = 0.008$, and $r = +0.591$, $p = 0.03$ for sniff Pes and sniff Pdi, respectively). A significant positive correlation was also observed between sniff Pdi and TwPdi ($r = +0.852$, $p = 0.002$), but ΔPgas/ΔPdi ratio did not correlated with sniff Pdi and TwPdi.

Comparison of Volumes and Pressures with Age

FRC was within the normal values for all the patients. In patients with DMD, a significant negative correlation was observed between FRC and age ($r = -0.523$, $p = 0.04$). In addition, age was inversely correlated with $\dot{V}_E$ ($r = -0.627$, $p = 0.007$) and FVC ($r = -0.72$, $p = 0.004$). A significant negative correlation was also observed between age and sniff Pes ($r = -0.613$, $p = 0.007$), sniff Pdi ($r = -0.589$, $p = 0.01$; Figure 1A), and Pgas cough ($r = -0.824$, $p < 0.0001$; Figure 2A).

The evolution of lung volumes and pressures was different in the patients with spinal amyotrophy and congenital myopathy. Indeed, no correlation was observed in the patients with spinal amyotrophy between age and FRC, $\dot{V}_E$, and the different respiratory muscle tests. Correlation was not calculated for FVC because only four patients were able to perform the FVC maneuver. In the patients with congenital myopathies, age was inversely correlated with $\dot{V}_E$ ($r = -0.653$, $p = 0.02$) but not with FRC and FVC. A significant positive correlation was observed between age and sniff Pes ($r = +0.556$, $p = 0.04$), but not with sniff Pdi and Pgas cough. However, when the patients with spinal amyotrophy and congenital myopathy were combined, a significant positive correlation was observed between age and sniff Pdi ($r = +0.552$, $p = 0.0095$; Figure 1B) but not with Pgas cough (Figure 2B).

Comparison of FVC with Respiratory Muscle Strength

In patients with DMD, a significant correlation was observed between FVC and ΔPgas/ΔPdi, sniff Pdi, sniff Pes, and Pgas cough (Table 4). The correlation between FVC and sniff Pdi is represented in Figure 3A. There was only a trend relationship between TwPdi and FVC ($r = +0.586$, $p = 0.0583$).

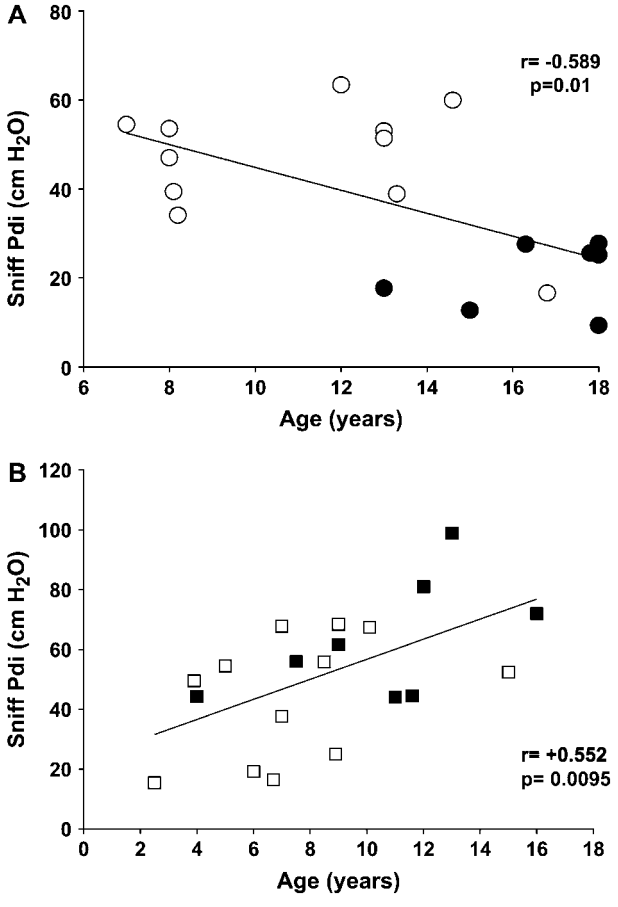

Figure 1. Correlation between transdiaphragmatic pressure during sniff and age. (*A*) A significant negative correlation was observed between transdiaphragmatic pressure during sniff (sniff Pdi) and age in the 20 patients with Duchenne muscular dystrophy. *Open circles*: patients not treated by noninvasive positive pressure ventilation; *closed circles*: patients treated by noninvasive positive pressure ventilation. (*B*) Transdiaphragmatic pressure during sniff (sniff Pdi) was not correlated with age in the patients with spinal amyotrophy (*closed squares*) and the patients with congenital myopathies (*open squares*) when analyzed separately, but a positive correlation was observed when the two groups were combined.

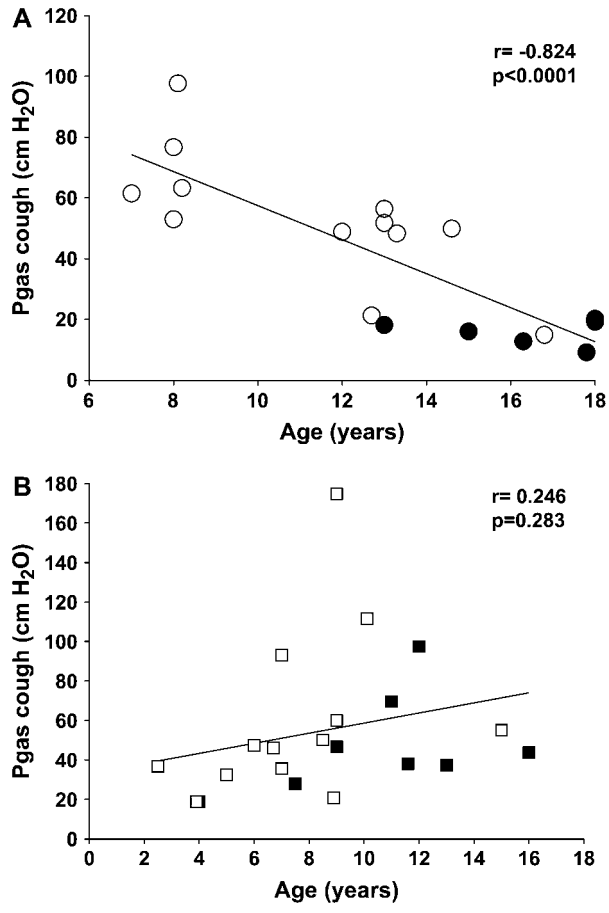

Figure 2. Correlation between gastric pressure during cough and age. (*A*) A significant negative correlation was observed between gastric pressure during cough (Pgas cough) and age in the 20 patients with Duchenne muscular dystrophy. *Open circles*: patients not treated by noninvasive positive pressure ventilation; *closed circles*: patients treated by noninvasive positive pressure ventilation. (*B*) Gastric pressure during cough (Pgas cough) was not correlated with age in the patients with spinal amyotrophy (*closed squares*) and the patients with congenital myopathies (*open squares*).

TABLE 4. CORRELATION OF FORCED VITAL CAPACITY WITH INDEXES OF RESPIRATORY MUSCLE PERFORMANCE

	DMD (*n* = 14)		Congenital Myopathy (*n* = 7)	
Respiratory muscle performance	*r*	p	*r*	p
ΔPgas/ΔPdi	0.614	0.026	0.613	0.143
Sniff Pes	0.603	0.029	0.863	0.012
Sniff Pdi	0.683	0.010	0.984	< 0.0001
Pgas cough	0.749	0.003	0.643	0.119
TwPdi	0.586	0.058	0.872	0.024

Definition of abbreviations: DMD = Duchenne muscular dystrophy; Pdi = transdiaphragmatic pressure; Pes = esophageal pressure; Pgas = gastric pressure; ΔPgas/ΔPdi = ratio of gastric pressure swing to transdiaphragmatic pressure swing during spontaneous breathing; TwPdi = transdiaphragmatic pressure obtained by the magnetic stimulation of the phrenic nerves.

In patients with congenital myopathy, FVC also correlated with sniff Pdi ($r = 0.984$, $p < 0.0001$; Figure 3B), sniff Pes ($r = 0.863$, $p = 0.01$), and TwPdi ($r = 0.872$, $p = 0.02$), but not with ΔPgas/ΔPdi and Pgas cough. Because of the small number of patients with spinal amyotrophy who were able to perform FVC (n = 4), no correlation could be established. But the results of these patients are represented in Figure 3B.

Comparison of the Unventilated and Ventilated Patients with DMD

Eight patients were treated by NPPV (NPPV group) for periods ranging from 2 mo to 6 yr (mean duration, 19 ± 28 mo). Indications for NPPV were as follows: diurnal hypercapnia in three patients, respiratory failure requiring invasive ventilation in one patient, nocturnal hypercapnia with clinical symptoms of sleep-disordered breathing in two patients, and a FVC less than 30% of predicted value in six patients. The mean age of the patients in the NPPV group was significantly older than those of the 12 patients who were not treated by NPPV (unventilated group; Table 5). As expected, the mean sniff Pes, sniff Pdi, and Pgas cough values were significantly lower in the NPPV group (Table 5). With regard to the magnetic stimulation of the phrenic nerves, although there was a trend showing lower values in the NPPV group than in the unventilated group, this difference was not statistically significant. The mean ΔPgas/ΔPdi during quiet breathing was significantly lower in the NPPV group, compared with the unventilated group (Table 5). FVC was significantly lower in the NPPV group compared with the unventilated group and there was also a trend for mean Pa_{O_2} to be lower in the NPPV group ($p = 0.052$). Finally, no difference was observed between the two groups with regard to V_T, respiratory rate, $\dot{V}_E$, FRC, Pa_{CO_2}, and any index of respiratory muscle output (data not shown).

Also, the three patients who were still able to walk had stronger respiratory muscles than the other patients with a mean sniff Pdi of 49 ± 9 cm H_2O, a mean TwPdi of 10 ± 4 cm H_2O, and a mean Pgas cough of 79 ± 18 cm H_2O. Two of these young patients were able to perform FVC maneuvers with values of 90 and 60% predicted.

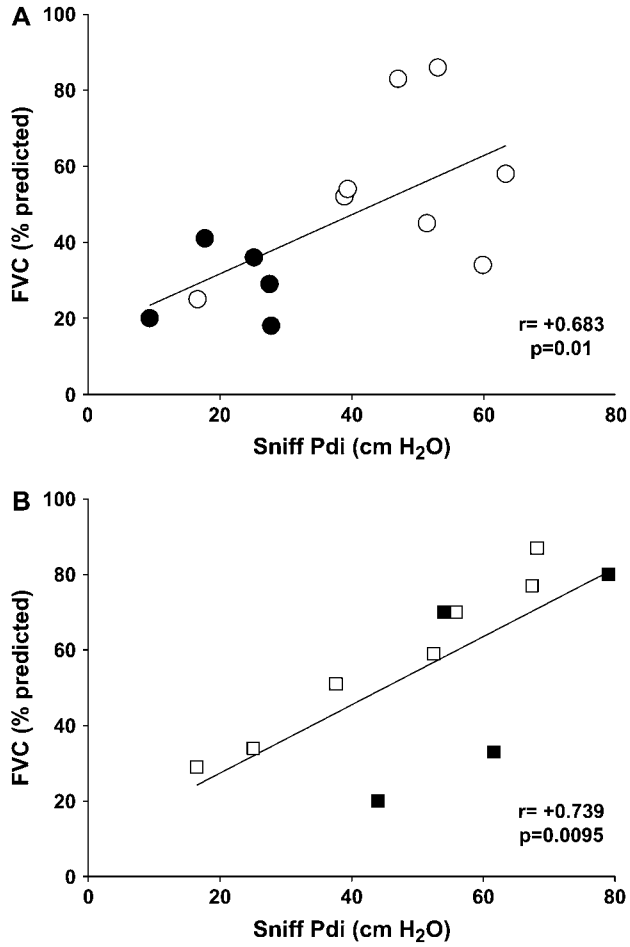

Figure 3. Correlation between vital capacity and transdiaphragmatic pressure during sniff. (*A*) A significant positive correlation was observed between forced vital capacity (FVC) and transdiaphragmatic pressure during sniff (sniff Pdi) in 14 patients with Duchenne muscular dystrophy. *Open circles*: patients not treated by noninvasive positive pressure ventilation; *closed circles*: patients treated by noninvasive positive pressure ventilation. (*B*) A significant correlation was observed between FVC and transdiaphragmatic pressure during sniff (sniff Pdi) in the seven patients with congenital myopathy (*open squares*). The four patients with spinal amyotrophy are represented by the *closed squares* (and were not included in the regression analysis). However, sniff Pdi was correlated with age when both populations were gathered.

DISCUSSION

This study shows that invasive volitional and nonvolitional respiratory muscle testing is feasible in young patients with DMD and other neuromuscular disorders. This is the first study that has quantified inspiratory and expiratory muscle strength in these young patient populations. The course of respiratory muscle weakness differed between the patients with DMD and the two other groups. Indeed, in patients with DMD, we demonstrated a correlation between increasing age and a fall in inspiratory and expiratory muscle strength as well as ventilation. This progression of respiratory muscle weakness with age was not observed in patients with spinal amyotropy and congenital myopathy. But in all groups, a correlation was observed between the measurements obtained by invasive volitional and nonvolitional respiratory muscle testing. An excellent correlation was also observed between the respiratory muscle tests and FVC. For the majority of the patients, respiratory muscle tests were easier to perform than FVC, supporting their usefulness in the assessment of young patients with DMD and other neuromuscular disorders.

Feasibility of Respiratory Muscle Testing

We used simple, "natural" maneuvers to assess inspiratory and expiratory muscle performance in these young children. Indeed,

TABLE 5. COMPARISON OF PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY NONVENTILATED AND VENTILATED BY NASAL POSITIVE-PRESSURE VENTILATION

	Unventilated Group ($n = 12$)	Ventilated Group ($n = 8$)	p Value
Age, yr	11.2 ± 3.2	16.5 ± 2	0.002
Sniff maneuver, cm H_2O			
Pes	47 ± 12	25 ± 8	0.002
Pdi	47 ± 13	21 ± 8	0.002
Pgas	−1 ± 10	−5 ± 4	0.052
Cough maneuver, cm H_2O			
Pgas cough	54 ± 22	17 ± 4	0.002
Tw maneuver, cm H_2O			
Pes	7 ± 4	4 ± 2	0.090
Pdi	10 ± 5	5 ± 2	0.068
Pgas	4 ± 2	1 ± 1	0.019
Breathing pattern, lung function, and gas exchange			
ΔPgas/ΔPdi	−0.06 ± 0.26	−0.32 ± 0.36	0.042
Cdyn, ml/cm H_2O	68 ± 37	43 ± 26	0.076
FVC, % predicted*	55 ± 23	26 ± 12	0.020
Pa_{O_2}, mm Hg	96 ± 6	85 ± 12	0.052
Pa_{CO_2}, mm Hg	37 ± 1	38 ± 4	NS

Definition of abbreviations: Cdyn = dynamic lung compliance; NS = not significant; Pes = esophageal pressure; Pdi = transdiaphragmatic pressure; Pgas = gastric pressure; ΔPgas/ΔPdi = ratio of gastric pressure swing to transdiaphragmatic pressure swing during spontaneous breathing; Tw = pressure obtained by the magnetic stimulation of the phrenic nerves.

Data are presented as mean ± SD.

* FVC was obtained in 14 patients.

the sniff maneuver is an easy volitional test to assess inspiratory muscle strength, which has proved its feasibility and reproducibility in young children, especially when associated with visual feedback (7, 8, 27). The cough maneuver is also a "natural" maneuver that has proved its usefulness in adult patients (9). Here also, visual feedback contributes to the maximality and the reproducibility of the test. The cough maneuver has been validated as a test to monitor expiratory muscle performance by means of the measurement of peak cough flow (28, 29), but the measurement of Pgas during a cough is even simpler than the recording of flow.

During these tests, intrathoracic and abdominal pressures were measured by means of a catheter with two integrated pressure transducers. These invasive measurements may be distressing for a relatively young and frail group of patients, such as young patients with neuromuscular disorders. However, we have found that the acceptance of these tests by the patients was good. Indeed, the insertion of this catheter, after topical anesthesia, was straightforward and without complication. The catheter is well tolerated because of its small external diameter combined with a soft and pliable nature. In fact, over the years, we have acquired an experience with this catheter, both in infants (30) and patients with lung disease, such as cystic fibrosis (18, 31–33), a group of patients that often insert the catheter themselves. In practice, the duration of the respiratory muscle assessment does not exceed 25 to 30 min, which obviously contributes to the acceptance and tolerability of these invasive tests.

Respiratory Muscle Weakness in DMD

Our results show that weakness of the diaphragm is detectable early in this group of patients with DMD. Indeed, ΔPgas/ΔPdi is an index that reflects the relative contribution of the diaphragm to tidal breathing (34). Inspiratory changes in pleural pressure (evaluated in the present study on Pes) and Pgas, and therefore Pdi, depend on the action and interaction of three groups of muscles: the diaphragm, the inspiratory intercostal and accessory muscles, and the abdominal muscles. When the inspiratory intercostal muscles contract, expanding the rib cage, while the diaphragm tenses without moving, ΔPgas/ΔPdi is zero. A negative ΔPgas/ΔPdi signifies paradoxical movement of the diaphragm (i.e., the diaphragm moves in a cephalad direction during inspiration). Thus, the more negative ΔPgas/ΔPdi, the greater the weakness of the diaphragm compared with the other inspiratory muscles. The advantage of this index is that it does not require any patient cooperation once the esophageal catheter is positioned correctly. In these patients with DMD, the decrease in sniff Pdi and TwPdi progressed with age as expected. Furthermore, weakness of the inspiratory and expiratory muscles coexisted, but a steeper gradient of decline with age was observed in the expiratory than in the inspiratory muscles.

This weakness of the inspiratory muscles translates into a decrease in alveolar ventilation. Indeed, the ability to sustain spontaneous ventilation can be viewed as a balance between neurologic mechanisms controlling ventilation together with respiratory muscle power (i.e., the respiratory muscles, on one side, and the respiratory load, determined by lung, thoracic, and airway mechanics, on the other). If ventilatory muscle power or central respiratory drive is too low and/or the respiratory load is too high, ventilation may be inadequate, resulting in alveolar hypoventilation and hypercapnia.

Interestingly, respiratory muscle output was moderately increased in these patients with DMD, as reflected by the increase in their WOB, PTPes, and PTPdi. With regard to the balance between load and capacity, this suggests that respiratory failure in DMD does not exclusively arise because of respiratory muscle weakness but is also a consequence of an increase in load. We acknowledge that the use of a theoretic value for the chest wall compliance represents a limit of our study because it certainly overestimates the real compliance in these patients who may have scoliosis, reduced chest wall compliance, and overweight (2). However, the values of these indices of respiratory effort were not associated with age, the necessity of ACE inhibitor treatment, or the use of NPPV.

As expected, all indices of inspiratory and expiratory muscles were weaker in the NPPV group than in the unventilated group. The decrease of inspiratory muscle performance in the NPPV group was associated with an increase of the paradoxical movement of diaphragm as suggested by the ΔPgas/ΔPdi, which was significantly more negative in the NPPV group than in the unventilated group. This increase in paradoxical motion of the diaphragm in the NPPV group was associated with a lower mean V_T and $\dot{V}_E$ in this group. All these observations suggest an imbalance between the inspiratory muscle performance and the energy expenditure that this subgroup has to produce to maintain adequate $\dot{V}_E$, which indirectly supports the need of NPPV in this subgroup. The efficacy of NPPV was demonstrated by the absence of hypercapnia in the NPPV group (35–37). The mean level of Pa_{O_2} was significantly lower in the NPPV group than in the unventilated group. This also shows that NPPV is able to reduce or normalize hypercapnia, but does not represent the treatment of hypoxemia in patients with neuromuscular disease. Finally, the decrease of lung compliance and of Pa_{O_2}, without concomitant increase of Pa_{CO_2} in the NPPV group, could be explained by the presence of microatelectasis in this more severe group, as previously discussed in the literature (38). Also, the three patients who were still able to walk had preserved respiratory muscle strength and lung volumes. This may suggest that, in patients with DMD, respiratory muscle testing may be postponed until the patients become wheelchair bound.

Respiratory Muscle Weakness in Spinal Amyotrophy and Congenital Myopathy

The involvement of the respiratory muscles is clearly different in patients with spinal amyotrophy and congenital myopathy. Our results show the preservation of diaphragm strength in patients with spinal amyotrophy with a positive ΔPgas/ΔPdi, a mean sniff Pdi of 63 ± 20 cm H_2O, and a mean TwPdi of 16 ± 8 cm H_2O. Patients with congenital myopathy represent a heterogeneous group of patients, having an intermediate pattern of respiratory muscle weakness. As opposed to patients with DMD, no significant progression of respiratory muscle weakness was observed with age in these two groups of patients.

Respiratory Muscle Tests Compared with the "Gold Standard" FVC

Presently, respiratory function in patients with DMD is monitored by routine measurement of FVC (5). The limitations and the difficulties associated with this measure are supported by the present study. Indeed, 6 of the 20 patients with DMD and 10 of the 21 patients with other neuromuscular disorders were not able to perform reliable and reproducible FVC maneuvers, whereas all the patients, even the youngest and those with moderate mental retardation, were able to perform adequate respiratory muscle tests. In the group of 14 patients with DMD, we observed a good correlation between the tests evaluating the inspiratory (sniff Pes and sniff Pdi) and expiratory (Pgas cough) muscle strength. Interestingly, the correlation between FVC and sniff Pes and sniff Pdi was linear. Based on the shape of the normal pressure–volume curve, one would expect a considerable loss of respiratory muscle strength before observing a fall in FVC and other lung volumes (39). In reality, patients with chronic respiratory muscle weakness display a greater than expected loss in FVC. This is due to the associated decrease in Cdyn, consequent to diffuse microatelectasis, and a decrease in chest wall compliance, probably due to stiffening of ribcage ligaments and ankylosis of the costovertebral and thoracovertebral joints.

Limitations of the Study

Limitations of our study are the absence of control data, which are difficult to obtain in young children, and the relatively small number of patients, especially in the spinal amyotrophy group. The increase in the number of patients with DMD may strengthen borderline associations such as lower TwPdi, Cdyn, and Pa_{O_2} values in the NPPV group. Finally, our calculation of the respiratory effort certainly underestimated the real respiratory muscle output because of the limits we underlined above. Finally, this cross-sectional study is not able to give individual data on rates of progression of respiratory muscle performance.

In summary, the widespread use of these invasive respiratory muscle tests has been restricted because they are considered more technically demanding than conventional noninvasive methods. However, in the current study, invasive "simple" sniff and cough maneuvers were easier to perform in young patients with neuromuscular disorders than the traditional volume measurements. Interestingly, in this young population, we observed an excellent correlation between the invasive volitional and nonvolitional tests, which excludes the need for expensive magnetic stimulators and coils. FVC, in those patients who were able to do the test, was of similar value to the respiratory muscle tests. Therefore, respiratory muscle tests confirm their usefulness in young patients with various neuromuscular disorders in the evaluation of respiratory muscle weakness.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the manuscript.

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