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Abdominal volume contribution to tidal volume as an early indicator of respiratory impairment in Duchenne Muscular Dystrophy

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ABSTRACT

Duchenne muscular dystrophy (DMD) is characterized by progressive loss of muscular strength that leads to a progressive restrictive pulmonary syndrome but it is still not clear if this determines alterations in the breathing pattern.

We studied 66 DMD patients at different stages of the disease (mean age 12.6±0.6, from 5 to 22 years), subdivided into 4 groups according to age, and 21 age-matched healthy male controls. Spirometry, lung volumes and nocturnal oxygen saturation were measured in all DMD patients. Ventilatory pattern and chest wall volume variations were assessed by optoelectronic plethysmography during spontaneous breathing both in seated and supine positions.

Whilst in a seated position no significant differences were found between patients and controls or between different age groups, in the supine position the average contribution of abdominal volume change to tidal volume (ΔVab%) progressively decreased with age ($p<0.001$). The patients who showed nocturnal hypoxemia showed significantly lower ΔVab%.

In conclusion, chest wall motion during spontaneous breathing in awake conditions and in supine position, provides important indicators regarding the degree of respiratory muscles impairment in DMD. ΔVab% is an important marker not only of the progression of the disease, but also an early indicator of nocturnal hypoxemia.

Word count: 197

Keywords: Duchenne muscular dystrophy, chest wall, abdomen, diaphragm, hypoxemia breathing pattern

INTRODUCTION

Duchenne Muscular Dystrophy (DMD), a lethal progressive muscle wasting disease with an incidence of 1 in 3500 live male births [1, 2] is associated with loss of muscle function over time. Loss of respiratory muscle strength, with ensuing ineffective cough and decreased ventilation, leads to pneumonia and respiratory insufficiency both during sleep and while awake.

Respiratory failure is due to the loss of respiratory muscle strength causing reduced lung and chest wall compliance, decreased ventilation, alveolar hypoventilation, ineffective cough, hypercapnia and hypoxemia [3, 4, 5] and is the commonest cause of death in DMD patients, usually when there is a severe and generalized disability.

The onset of respiratory insufficiency can be subtle, and most patients with DMD are not aware that they have lost respiratory muscle strength and that their cough is less effective.

Traditionally, respiratory evaluation in DMD patients includes patient history and physical examination, measurements of pulmonary function, and assessment of sleep-disordered breathing. Up to now respiratory problems in DMD have been mainly described in terms of reduction of vital capacity [6] and inspiratory muscles weakness [7, 8, 9]. These descriptors, although very useful, are not the unique determinants of the worsening of respiratory function in DMD. In fact, it has been reported [10] that some patients with extremely low values of vital capacity can breathe autonomously, while others need constant ventilatory support.

In addition, there are difficulties associated with the methods currently used to assess respiratory function in DMD patients. Volitional tests of lung and respiratory muscle function, such as spirometry and maximal respiratory pressure tests, require a high level of patient cooperation. Other methods, based on pressure measurements and magnetic and/or electrical stimulation of the respiratory muscles, are more invasive and are not well tolerated by the patients.

The aim of the present study was to determine if detailed analysis of chest wall kinematics could identify new parameters associated with respiratory aspects of disease progression. To achieve this goal we used Opto−Electronic Plethysmography (OEP) [11, 12, 13], a technique which does not require patient collaboration and allows a completely noninvasive breath−by−breath measurement of chest wall volume and its different compartments. We tested the hypothesis that in DMD the progressive loss of respiratory muscle strength determines alterations in the pattern of spontaneous breathing that precede and anticipates the onset of nocturnal hypoxemia and respiratory failure.

PATIENTS AND METHODS

PATIENTS

Sixty-six patients affected with Duchenne Muscular Dystrophy were recruited. The diagnosis was made on the basis of traditional diagnostic criteria: progressive muscular deficit resulting in severe motor disability, increased muscle plasma enzymes, muscle biopsy identifying muscular degeneration and absence of dystrophin, alterations in the DMD gene (deletions, duplications or point mutations) [2].

DMD population was subdivided into 4 groups according to age: group I (≤ 7 yrs); group II (≥ 8 and ≤ 12 yrs); group III (≥ 13 and ≤ 16 yrs); group IV (≥ 17 yrs) (table 1).

Twenty-one healthy male subjects (average age 13.5 ± 1.4 years, height 158 ± 5 cm, weight 52 ± 6 kg) were recruited as control group and subdivided according to the same age groups. Four subjects were aged < 7 yrs (average age 5.0 ± 0.4 years, height 117 ± 5 cm, weight 22 ± 3 kg), five subjects were aged between 8 and 12 years (average age 9.4 ± 0.4 years, height 139 ± 2 cm, weight 32 ± 2 kg), six subjects were aged between 13 and 16 years (average age 15± 0.5 years, height 174 ± 3 cm, weight 61 ± 6 kg) and six subjects were aged > 17 years (average age 21.1 ± 1.8 years, height 179 ± 2 cm, weight 80 ± 8 kg).

Within group I, all patients were still ambulant, without scoliosis or heart dysfunction.

Within group II, 7 patients were still ambulant and 8 were presenting scoliosis: 2 patients mild (Cobb angle < 20°), 4 patients moderate (Cobb angle between 20° and 40°), 2 patients severe (Cobb angle >40°) scoliosis; two patients were presenting mild or severe heart dysfunction.

In group III, 11 patients were presenting scoliosis (3 mild, 5 moderate and 3 severe) and one underwent spinal fusion; heart dysfunction was observed in 6 patients (1 mild and 5 moderate).

In group IV, 13 patients presented with scoliosis (8 mild, 4 moderate and 1 severe) and 2 underwent spinal fusion. Only one patient was under treatment with nocturnal non-invasive ventilation (NIV). Heart dysfunction was present in 10 patients (2 mild, 7 moderate and 1 severe).

All patients with cardiac dysfunction (independently of the group) were under β-blockers or ACE inhibitors or both treatment. None of the patients presented symptoms of additional diseases such as cerebral palsy, behavioural and/or psychiatric disturbances, acquired brain or spinal injuries, epilepsy, allergies or asthma.

All patients (or parent of the patient in the case of children) signed a written informed consent form, as approved by the Local Ethical Committee of IRCCS "E. Medea" Institute. The study was approved by the Institute's Human Ethics Committee according to the declaration of Helsinki.

METHODS

Pulmonary function tests

Measurements of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) were performed in seated position with a flowmeter attached to a flanged rubber mouthpiece with the nose occluded (Vmax series 22, SensorMedics, Yorba Linda, USA). Subdivision of lung volumes (Functional Residual Capacity, FRC; Residual volume, RV and Total Lung Capacity, TLC) was measured by the nitrogen washout technique (Vmax series 22, SensorMedics, Yorba Linda, CA).

Nocturnal pulse-oxymetry (Nonin, 8500 digital pulse oximeter Quitman, TX) was performed in all patients.

Kinematic analysis

Kinematics of the chest wall and its different compartments was studied by using Optolectronic Plethysmography (OEP) (OEPSystem, BTS, Milan, Italy) both in the supine [11, 12] and seated position [13]. Fifty-two reflective markers were placed over the anterior chest wall surface from clavicles to pubis and after a period of adaptation, patients were analyzed in the supine position during three minutes of spontaneous quiet breathing in awake diurnal state.

For the measurement in the seated position, an 89 marker configuration, as described in reference 13, was used in the healthy subjects and in the DMD patients who were able to maintain a static trunk position. For patients analyzed while seated in a wheelchair, the same marker configuration as adopted for the analysis in the supine position was used.

Each marker was tracked in three dimensions by eight special infrared video cameras positioned around the patient at a sampling rate of 60 Hz. For volume computation, the chest wall surface was approximated by a set of triangles connecting the markers and standard algorithms provided the measurement of the total chest wall volume (V_{CW}) and its different thoraco−abdominal compartments: pulmonary rib cage ($V_{RC,P}$, where the action of inspiratory and expiratory rib cage muscle is present), abdominal rib cage ($V_{RC,A}$ where the diaphragm is attached) and the abdomen (V_{AB}, where both the diaphragm and the expiratory abdominal muscles act) [14, 15].

From total and compartmental chest wall volume tracings, the following parameters were considered: tidal volume (V_T) as the average total chest wall volume variations, respiratory rate (RR), minute ventilation and percentage contribution of the different compartments to tidal volume.

STATISTICAL ANALYSIS

Differences between the four groups of DMD when control data were not available (such as for spirometric and subdivision of lung volume data) were evaluated by parametric one-way Analysis Of Variance (ANOVA), with age group as the independent factor. In the cases where the data were not normally distributed a non-parametric Kruskal-Wallis one-way ANOVA on ranks was applied. Differences between the four groups of DMD, when control data on healthy subjects were available (such as for ventilator parameters and kinematic data), were assessed by the same two-way ANOVA test, with age and pathology as the independent factors. Post-hoc tests were based on Holm-Sidak and Dunn methods, for parametric and non parametric ANOVA tests respectively.

To compare data between groups of patients with nocturnal hypoxemia (DeSat group, see below) and all DMD patients belonging to groups III and IV, an unpaired Student t-test and a Mann-Whitney Rank Sum test were applied where the data were and were not normally distributed , respectively.

Finally, to compare data between groups of patients with different severity of kyphoscoliosis (present or absent) in the different age groups a two-way ANOVA test was performed.

The p-values reported in the result section are the result of the one- or two-way ANOVA tests. In fig. 4 and 5, the result of the post-hoc analysis is indicated.

All data are expressed as mean ± SE. Differences were regarded as significant with p-values ≤ 0.05.

RESULTS

Pulmonary function

In table 1 the results of pulmonary function tests are shown as average values of the different groups. Only two patients belonging to group I could perform a reliable spirometry, due to poor collaboration in performing the maneouvers and/or in keeping the mouthpiece in place. Therefore representative mean values for group I are not reported. A progressive reduction of FVC, FEV_1 and PEF average values was observed with increasing age when expressed as percentage of predicted values ($p<0.001$). Conversely, subdivision of lung volume data showed a significant trend between the different groups only when expressed as absolute values, increasing from groups II to group IV (TLC, $p=0.043$; RV and FRC, $p<0.001$).

In table 1 the results of nocturnal oxygen saturation measurements are also reported as a percentage of the night-time spent with SpO_2 between 95% and 100%, between 90% and 94% and lower than 90%. Ten patients, 3 belonging to group III and 7 to group IV, spent at least 10% of the night time with $SpO_2<95\%$. These patients were considered as forming a further group for following analysis (DeSat group) and were compared to the overall group of patients belonging to groups III and IV.

Figures 2A and 2B show the progressive decreasing average values of FVC and FEV1 (expressed as percentage of predicted values) in the different groups. Patients of subgroup DeSat presented averaged values (31.9±22.1% and 30.9±24.9%, respectively) lower than the overall groups III and IV but the difference did not reach statistical significance ($p= 0.109$ and $p=0.085$, respectively).

The same behavior was observed for TLC and RV average values (fig. 3A and 3B). Patients belonging to subgroup DeSat showed average values (50.4±26.7% and 106.1±55.7, respectively) that were not statistically different to the overall groups III and IV data ($p= 0.081$ and $p=0.378$, respectively).

Ventilatory pattern

In figure 4 the mean breathing frequency, tidal volume and minute ventilation are shown for both controls and DMD patients in supine (left panels) and seated (right panels) positions.

In the supine position, tidal volume of DMD patients in groups II and IV was significantly lower than normal ($p=0.012$ and $p=0.027$, respectively). Breathing frequency was only slightly different between controls and patients ($p=0.041$). Consequently, minute ventilation followed a similar pattern in both DMD patients and controls ($p = 0.088$) (fig. 4, left panels).

In the seated position, breathing frequency was independent of age ($p=0.295$) and no differences between DMD patients and healthy controls ($p= 0.953$) were present. Conversely, both tidal volume and minute ventilation increased with age ($p<0.001$) and were significantly higher in healthy controls than in DMD patients in the groups II, III and IV ($p<0.001$).

No differences were seen in these variables between patients in the DeSat subgroup and the overall groups III and IV, both in the supine and in the seated position.

Kinematic data

In the supine position, in group I the average contribution of abdominal volume variation to tidal volume was similar to that observed in healthy control subjects, but it progressively decreased with age from group I to group IV ($p<0.001$) (fig. 5a).

Figure 5b reports the percentage contribution of abdominal compartment to tidal volume in the DMD patients and healthy controls in a seated position. No significant differences were seen between patients and controls ($p=0.510$) or between different age groups ($p=0.863$).

Patients belonging to subgroup DeSat showed no differences in the abdominal contribution in a seated position, while a statistically significantly lower average value ($p<0.001$) compared to the overall groups III and IV was present in the supine position.

Figure 6 shows thoraco-abdominal kinematic analysis in a set of representative cases. With increasing age, the percentage contribution of abdomen to tidal volume progressively decreases

with a corresponding increase of rib cage contribution. This can be seen also on rib cage vs abdominal volume plots (bottom panels of fig. 6), in which the slope is progressively increasing and the loops become generally wider, suggesting an increased asynchrony between the rib cage and the abdomen. Within groups III and IV, this altered pattern was particularly evident in the patients belonging to subgroup DeSat.

The presence of scoliosis did not influence any of the ventilatory pattern measurements (tidal volume, breathing frequency and minute ventilation) or kinematic measurements (contribution of the different chest wall compartments to tidal volume) variables in either posture.

DISCUSSION

Early diagnosis of respiratory problems and especially respiratory muscle weakness is essential in the clinical care of DMD patients. This study, performed on a large number of DMD patients and healthy controls, showed that it is possible to identify subtle disease-stage in relation to changes in the breathing pattern of these patients that can be measured noninvasively.

During spontaneous breathing, significant differences between DMD patients and controls as well as between different age groups of DMD patients, clearly emerge only when the contribution of chest wall compartments to tidal volume is considered in the supine position. In this posture, the features of the ventilatory pattern in DMD patients follow a trend due to increasing age similar to that found in healthy subjects (fig. 4). As it was expected, tidal volume increases with age both in DMD patients as in those healthy controls, but less in DMD. The dystrophic patients tend to maintain a slightly higher frequency than healthy subjects which determines values of total minute ventilation similar to those of healthy subjects up to groups III and IV. This pattern indicates that DMD patients cope with the progression of the disease by adopting a strategy that allows them to maintain an adequate minute ventilation. However, striking differences emerge when the contribution of the different chest wall compartments to tidal volume is taken under consideration (fig. 5). In healthy subjects in the supine position the abdomen contributes to tidal volume on average by about 70% (and correspondingly the rib cage by about 30%), and this contribution does not depend on age. In DMD patients there is a progressive and significant ($p<0.001$) reduction from group I to group IV (from 70% to 40%, respectively) in the contribution of the abdomen, with a corresponding increase in the contribution of the rib cage compartment from 30% to 60%. Surprisingly, the presence of scoliosis did not influence any parameter in both postures. The only significant difference found in the seated position was in tidal volume and minute ventilation between DMD groups II, III and IV and controls. This finding may indicate that DMD patients of these 3 groups can hypoventilate with consequent elevation of arterial PCO_2 in this posture.

A limitation of the present study is that OEP measurements of abdominal and rib cage volume changes may be considered as indirect assessment of rib cage muscles and diaphragm function. We deliberately choose to avoid more invasive measurements such as oesophageal, gastric and transdiaphragmatic pressures in order to minimize invasivity and instrumentation of these techniques. For similar reasons other methods for the evaluation of inspiratory muscles function based on the assessment of transdiaphragmatic and esophageal pressures generated during volitional (sniff and cough maneuvers) and nonvolitional (magnetic or electrical stimulation of the phrenic nerve) tests [7, 8, 9] were not considered in the present study. Nevertheless, our data obtained in healthy subjects are fully consistent with those obtained in previous studies that showed a reduction of rib cage motion and an increase of abdominal excursion in the supine position relative to the sitting position [16, 17]. This is partly due to the increase in abdominal compliance and the decrease in rib cage compliance in this posture [18] and partly due to the different geometry of the diaphragm in the supine position [19] that is stretched by the viscera and consequently has a higher passive tension. In contrast, our DMD patients showed a behavior that changed with age , suggesting a progressive impairment of the diaphragm action. The fact that rib cage compartment contribution increases and abdominal compartment contribution decreases with increasing age may suggest that, in order to maintain minute ventilation within physiological ranges, DMD patients cope with the progressive impairment of the diaphragm by increasing the recruitment of the inspiratory rib cage muscles. However, presumably also inspiratory rib cage muscles (intercostals, parasternals, scalene and neck muscles) are progressively impaired like all skeletal muscles, the adopted strategy might be useful only over limited periods of time. To verify this hypothesis over long periods of time, longitudinal studies are ongoing. Another important result of the current study is the correlation that we found between the degree of nocturnal oxygen desaturation and the day time characteristics of breathing. Oxygen saturation significantly decreased during the night time in

a significant number of patients belonging to group III and IV. In these patients the abdominal contribution to tidal volume was significantly lower when compared to that of the overall group of patients belonging to groups III and IV. It is interesting to underline that this difference is present in supine, but not in the seated position. It must be emphasized that early signs of ventilatory problems, namely diaphragm impairment, initially occur only in the supine posture. It is known that in this position the diaphragm is the main contributor to tidal volume. It can be therefore hypothesized that only in the supine position will the effects of early signs of diaphragm impairment be initially observed,

The assessment of nocturnal hypoxemia is clinically relevant and it is currently considered as a marker of progression of the disease, and one of the indices used as guide for the intervention of NIV during night [20, 21]. Smith et al [22] showed that although awake minute ventilation is normal in DMD, hypoventilation occurs in all sleep stages, and those patients with diaphragmatic dysfunction are especially vulnerable to oxygen desaturation during REM sleep. Other previous observations also showed that sleep-related hypoventilation and hypoxemia occurs in presence of diaphragm dysfunction [23, 24] and is particularly evident in REM sleep, when muscular atonia is maximal and the diaphragm should be the only respiratory muscle active [23, 25, 26].

In conclusion, our study presents several novel issues. In first place, we considered a wide range of ages, focusing our attention on the different stages of the disease progression. We performed a noninvasive analysis during awake conditions and we found a relationship between the breathing pattern in these conditions and nocturnal variations of oxyhaemoglobin desaturation. Specifically, we found that the contribution of abdomen to total volume during spontaneous breathing in awake conditions seems to be a strong indicator of diaphragm impairment, which occurs at different times in different patients. These indicators are complementary to the assessment of respiratory function traditionally provided by spirometry [27, 28, 29] and have the great advantage of not requiring patient cooperation, motivation and coordination. We believe that our results are clinically relevant,

and will allow us to identify early a subgroup of patients in need of more attention and more frequent evaluations before eventually intervening with noninvasive mechanical ventilation

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FIGURE LEGENDS

Fig. 1 – Experimental set-up for the analysis of chest wall volumes by Opto-Electronic Plethysmography in supine (1A) and seated (1B).

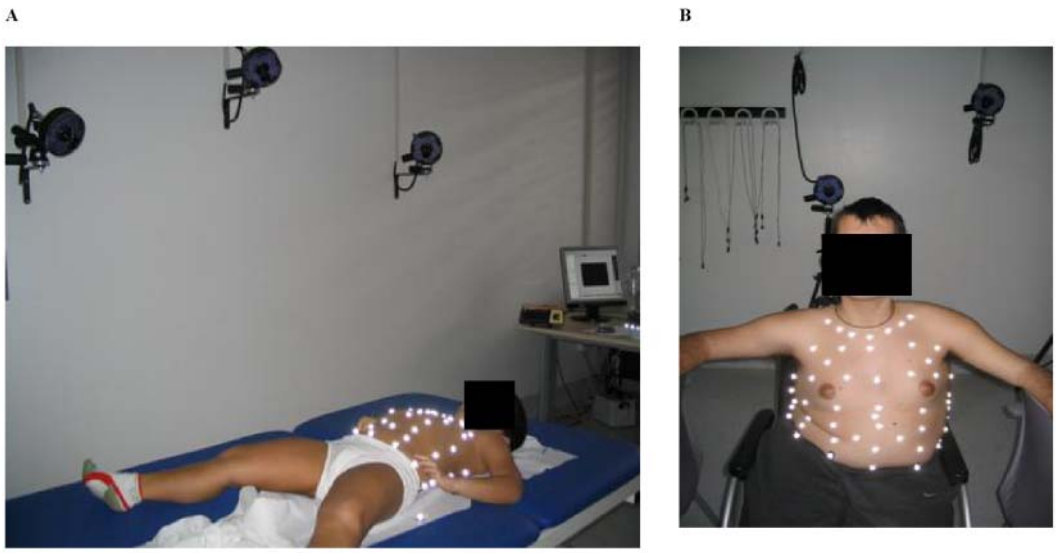
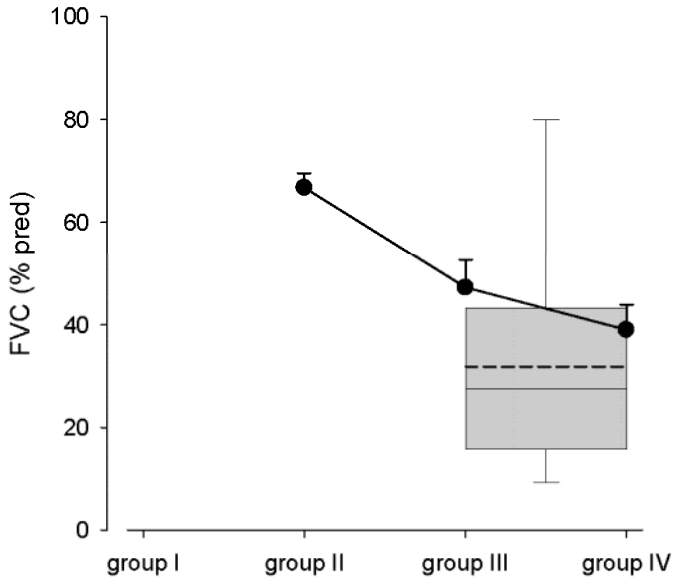


Fig.2 – Average values ± S.D. of forced vital capacity (FVC, % predicted values) (A) and forced expiratory volume in 1 sec (FEV_1, % predicted values) (B) in the different groups of DMD patients (see text). Whisker box plots indicate the distribution of FVC (A) and FEV1 (B) values in DMD patients belonging to group III and IV showing at least 10% of night time with SpO_2<95% (DeSat group). For each box, its boundary closest to zero indicates the 25th percentiles, the solid line and the dashed lines within the box marks respectively the median and the mean and the boundary of the box farthest from zero indicates the 75th percentile. Whiskers (error bars) above and below the box indicate the 90th and 10th percentiles. Data of patients belonging to group I are not available.

FIGURE 2

A


100
80
60
40
20
0
FVC (% pred)
group I
group II
group III
group IV

B

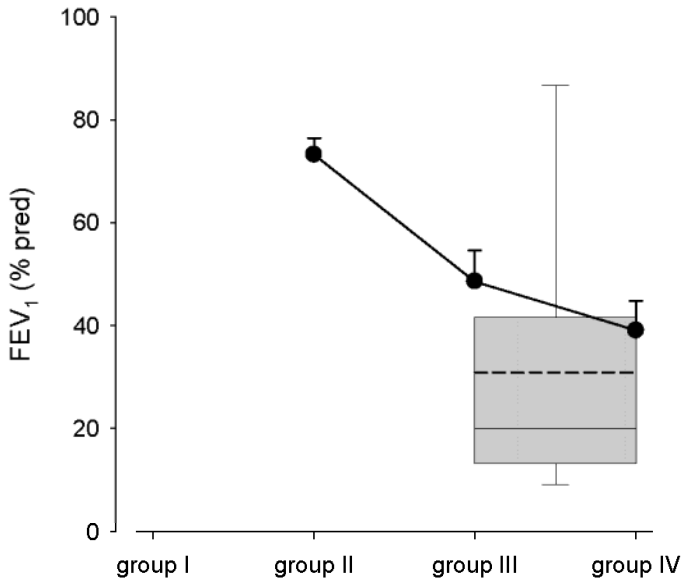
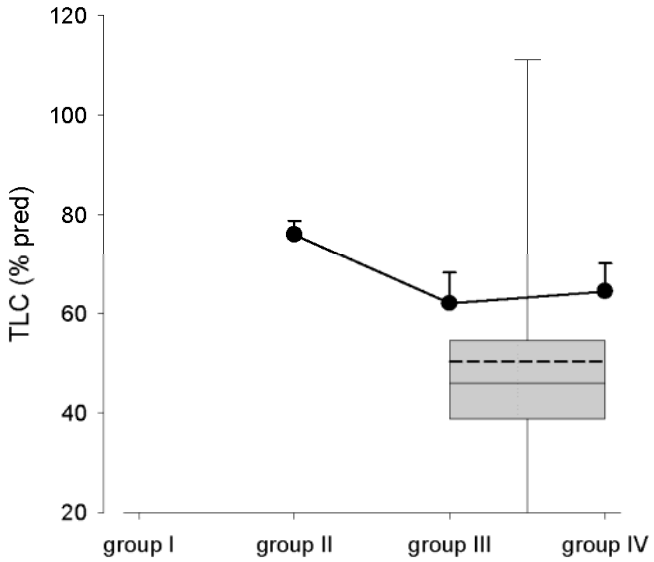

100
80
60
40
20
0
FEV1 (% pred)
group I
group II
group III
group IV

Fig.3 – Average values ± S.D. of Total Lung Capacity (TLC, % predicted values) (A) and residual volume (RV, % predicted values) (B) in the different groups of DMD patients (see text).

Whisker box plots indicate the distribution of TLC (A) and RV (B) values in DMD patients belonging to group III and IV showing at least 10% of night time with SpO_2<95% (DeSat group) *(see legend of fig. 2)*. Data of patients belonging to group I are not available.

FIGURE 3

A


120
100
80
60
40
20
TLC (% pred)
group I
group II
group III
group IV

B

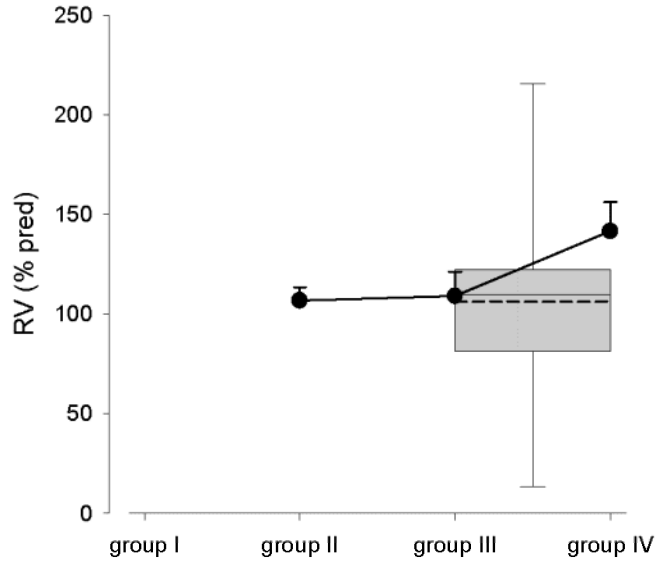

250
200
150
100
50
0
RV (% pred)
group I
group II
group III
group IV

Fig.4 – Average values ± S.D. of breathing frequency (A, top panels), tidal volume (B, middle panels) and minute ventilation (C, bottom panels) of the different age groups (see text) in supine (left panels) and seated (right panels) position. Closed circles: DMD patient; open circles: healthy subjects.

In each panel, whisker box plots indicate the distribution of the corresponding values in DMD patients belonging to group III and IV showing at least 10% of night time with SpO_2<95% (DeSat group) *(see legend of fig. 2)*.

**, ***: $p<0.01$, $p<0.001$ (vs group I);

°: $p<0.05$ (vs group II)

FIGURE 4

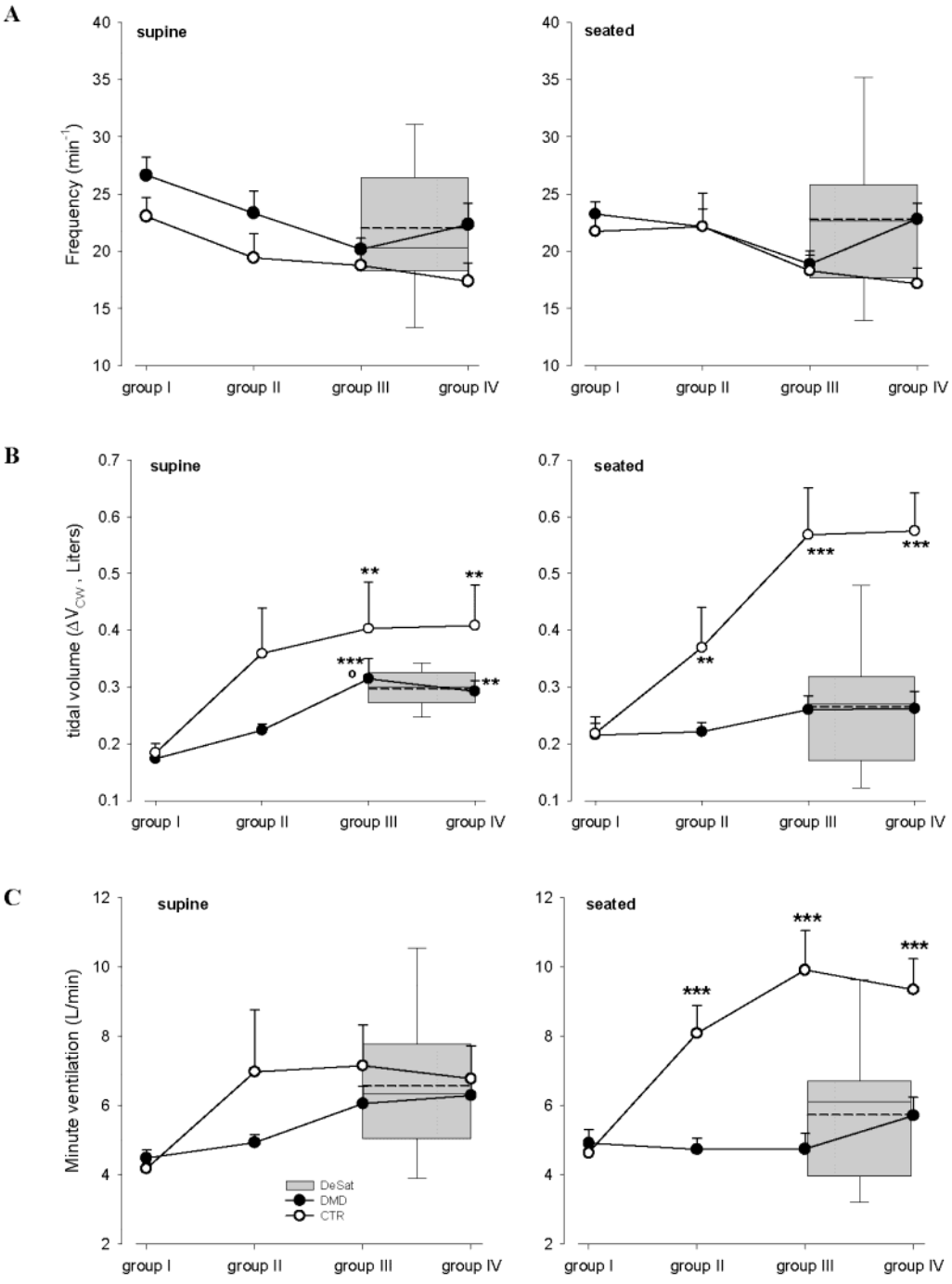

A
supine
seated
Frequency (min-1)
40
35
30
25
20
15
10
group I
group II
group III
group IV
B
supine
seated
tidal volume (ΔVCW , Liters)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
**
***
o
C
supine
seated
Minute ventilation (L/min)
12
10
8
6
4
2
DeSat
DMD
CTR

Fig.5 – Average values ± S.D. of abdominal tidal volume, expressed as percentage of total tidal volume (ΔV_{AB}) of the different age groups (see text) in supine (left) and seated (right) position. Closed circles: DMD patient; open circles: healthy subjects.

In each panel, whisker box plots indicate the distribution of ΔV_{AB} values in DMD patients belonging to group III and IV showing at least 10% of night time with SpO_2<95% (DeSat group) *(see legend of fig. 2)*.

**: p<0.01 (vs group I);

°°°: p=0.001 (vs group II);

ΔΔ: p<0.01 (vs group III)

FIGURE 5

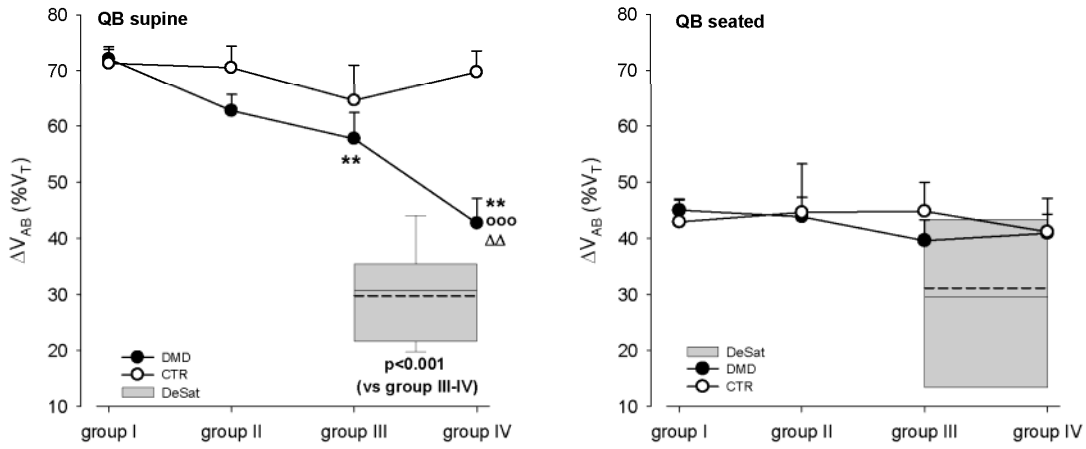


Fig. 6 - Representative cases of thoraco-abdominal volume changes during spontaneous breathing in supine position in a control healthy subject and in DMD patients belonging to groups I, II, III, IV and DeSat (from left to right).

Top panel: volume changes of the rib cage (ΔV_{RC}); middle panels: volume changes of the abdomen (ΔV_{AB}); bottom panels: rib cage vs abdominal volume changes plots. With increasing age, the percentage contribution of abdomen to tidal volume progressively decreases with a corresponding increase of rib cage contribution.

FIGURE 6

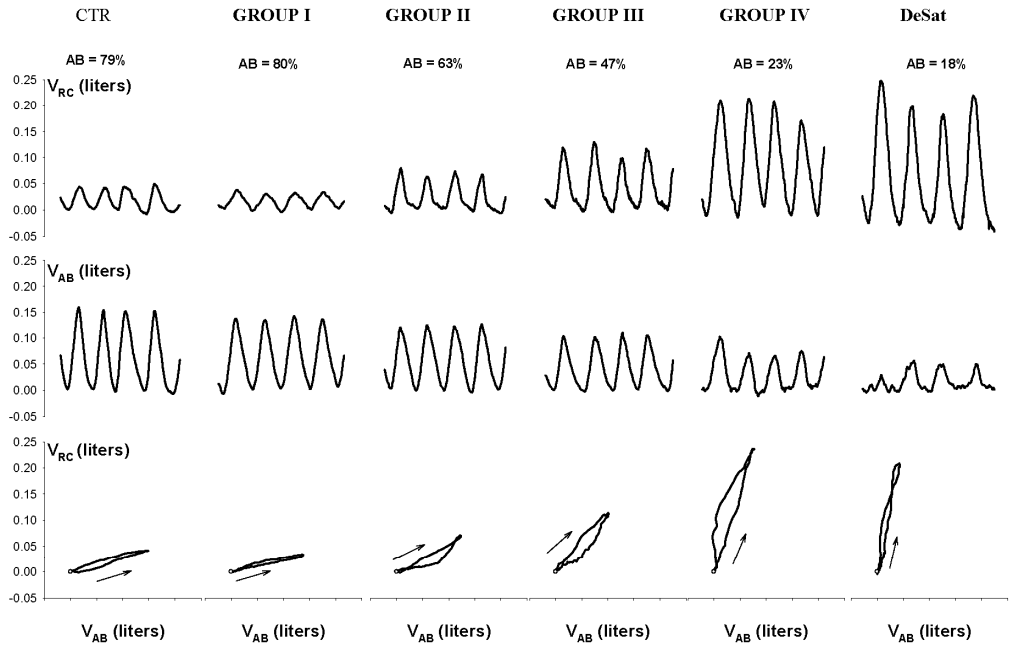


TABLE 1 – DMD patients' characteristics and pulmonary function test.

FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in 1 second; PEF, Peak Expiratory Flow; TLC, Total Lung capacity; RV, Residual Volume; FRC N_2 (Functional Residual Capacity assessed by N_2 washout); %SpO_2 100-95, %SpO_2 94-90, %SpO_2 <90,percentage of the night time spent with oxygen saturation respectively between 95% and 100%, between 90% and 94% and lower than 90%.

% pred: percentage of predicted value

Groups I, II, III and IV: see text.

P values refer to one-way ANOVA

	all	Group I	Group II	Group III	Group IV	p
N	66	13	23	15	15	
age (yrs)	12.64 ± 0.63	6.23 ± 0.59	10.74 ± 0.24	14.73 ± 0.32	19.00 ± 0.50	
height (cm)	145.65 ± 2.68	115.77 ± 6.63	142.00 ± 1.90	161.50 ± 2.30	162.30 ± 2.80	<0.001
weight (Kg)	45.16 ± 2.53	23.54 ± 4.04	44.18 ± 2.67	53.93 ± 4.16	58.47 ± 4.73	<0.001
BMI	20.37 ± 0.64	17.36 ± 1.92	21.55 ± 0.93	20.45 ± 1.26	21.84 ± 1.26	n.s.
SPIROMETRY						
N	55		23	15	15	
FVC (L)	1.60 ± 0.08		1.63 ± 0.07	1.74 ± 0.20	1.52 ± 0.17	n.s.
FVC (% pred)	53.30 ± 2.81		66.81 ± 2.78	47.27 ± 5.39	39.00 ± 4.95	<0.001
FEV_1 (L/sec)	1.41 ± 0.07		1.50 ± 0.07	1.45 ± 0.18	1.27 ± 0.15	n.s.
FEV_1 (% pred)	56.67 ± 3.32		73.24 ± 3.26	48.60 ± 5.98	39.07 ± 5.75	<0.001
FEV1/FVC (%)	86.3 ± 1.6		91.9 ± 1.15	84.1 ± 2.7	80.1 ± 4.5	=0.014
PEF (L/sec)	2.77 ± 0.13		2.93 ± 0.15	2.70 ± 0.29	2.68 ± 0.33	n.s.
PEF (% pred)	50.74 ± 2.89		63.71 ± 3.32	43.00 ± 4.30	36.73 ± 5.41	<0.001
LUNG VOLUMES						
TLC (L)	2.82 ± 0.12		2.54 ± 0.10	2.91 ± 0.31	3.28 ± 0.23	= 0.043
TLC (% pred)	68.98 ± 2.71		76.00 ± 2.74	62.00 ± 6.26	64.40 ± 5.71	n.s.
RV (L)	1.17 ± 0.08		0.87 ± 0.06	1.12 ± 0.13	1.69 ± 0.16	<0.001
RV (% pred)	117.89 ± 6.26		106.43 ± 6.74	108.73 ± 12.33	141.33 ± 14.64	n.s.
FRC N_2 (L)	1.59 ± 0.09		1.25 ± 0.07	1.57 ± 0.17	2.18 ± 0.18	<0.001
FRC N_2 (% pred)	81.21 ± 3.70		82.38 ± 4.41	70.13 ± 7.53	87.47 ± 8.29	n.s.

%SpO_2											
N	53		12		16		11		14		
100-95	91.53	± 2.47	98.67	± 0.47	79.25	± 9.61	84.45	± 8.85	84.43	± 5.55	= 0.014
94-90	7.68	± 2.21	1.33	± 0.47	2.25	± 0.72	12.73	± 7.39	14.93	± 5.46	= 0.008
<90	0.79	± 0.55	0.00	± 0.00	0.13	± 0.09	2.82	± 2.62	0.64	± 0.37	n.s.