Vol. **95** (2001) 898–903



# Lung function in children with Duchenne's muscular dystrophy

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**Abstract** Duchenne's muscular dystrophy (DMD), characterized by gradually developing muscular weakness, leads to respiratory symptoms and reduced lung function. We aimed to assess lung function in 25 patients with DMD in relationship to age and muscular function. The 25 boys, mean age 13 years, comprized patients in southern Norway with DMD, taking part in an epidemiological follow-up study. None had chronic respiratory disease. Lung function was measured by maximum expiratory flow–volume loops and whole body plethysmography, and repeated after 1 year ($n$=14). Lung function was reduced compared to predicted values for healthy children. Forced expiratory volume in 1 sec ($FEV_1$)% predicted and forced vital capacity (FVC)% predicted correlated (significantly) inversely to age. $FEV_1$ and FVC decreased annually 5·61 and 4·2% of predicted, respectively. Absolute values of FVC (litres) and $FEV_1$ ($l\,sec^{-1}$) increased until mean age 14 years, decreasing thereafter. Values in % predicted decreased steadily throughout the age range (6–19 years). Lung function correlated closely to upper limb muscle function. 

doi:10.1053/rmed.2001.1177, available online at http://www.idealibrary.com on IDEAL®

**Keywords** DMD; lung function; flow volume loops; body plethysmography; muscular function.

## INTRODUCTION

Duchenne's muscular dystrophy (DMD) is characterized by a gradually decreasing muscular strength, affecting all striated (including the respiratory muscles) and heart muscle (1). Symptoms present themselves before the age of 5 years; the main clinical signs being progressive symmetrical weakness with proximal limb muscles affected more than distal muscles (2). The progressive weakness leads to loss of ambulation before the age of 13 years (3) and severe scoliosis (4).

With increasing muscular weakness, a reduction in lung function occurs (5), and a relationship between pulmonary function and stage of disease has been described (6). The end-stage of the disease is characterized by increasingly severe respiratory complications and cardiac failure, in combination with severe locomotor problems (5,7). Measurements of respiratory function are important for the evaluation for therapeutic intervention (8) and the prognosis of the disease (9).

Various aspects of respiratory function have been assessed in relation to DMD, such as measures of maximum inspiratory and expiratory pressures to detect respiratory muscle weakness (3,5), lung volumes (by helium dilution spirometry) (5) and spirometry (3,5). It has in fact been maintained that forced vital capacity (FVC) best reflects clinical status (10).

The primary aim of the present study was to assess lung function as part of a follow-up study of children with DMD in southern Norway, including measures of maximum expiratory flow volume-loops and lung volumes. A secondary objective was to analyse changes in lung function in relation to the duration of the disease, the age of the children, and to their physical ability and muscle function.

Received 8 February 2001 accepted in revised form 21 June 2001, and published online 24 September 2001.

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## METHODS AND SUBJECTS

### Design of the study

As part of a major epidemiological follow-up study of children with DMD in southern Norway (11,12), the 25 boys included in the study underwent lung function testing by use of whole body plethysmograph and maximum expiratory flow-volume loops. A second lung function measurement was performed after an interval of 1 year, if possible.

The study was approved by the medical ethics committee, and the parents of the children included in the study gave informed consent.

## Subjects

Twenty-five boys with DMD with a median age of 13 years (range 6–19 years) were included into the study. Fourteen of the subjects underwent a second lung function measurement after 1 year with a median age of 14 years (range 8–20 years) at the time of the second measurement. Eleven children could not return for a second measurement because of the strain their long journey to the hospital (long distances) would have on their physical condition. Seven subjects (including the oldest boy aged 19 years) used assisted home ventilation (intermittent positive pressure ventilation via a face mask) during the night. None of the patients had any chronic lung disorders, and none reported pneumonia in the last year prior to the investigation. None of the subjects had undergone spinal surgery at the time of investigations.

## Methods

Lung function was measured by maximum expiratory and inspiratory flow–volume loops and whole body plethysmograph (Masterlab, Erich Jaeger GmbH & Co KG, Würzburg, Germany). Calibration of the equipment was performed daily according to manufacturer's instructions. The subjects breathed through a silicon mouthpiece between the teeth, with a rim inserted between the teeth and lips, ensuring that no leaks occurred during forced expiration. Measurements were performed according to recommendations of the European Respiratory Society (13). Forced expiratory volume during 1 sec ($FEV_1$), maximum expiratory flow at 75, 50 and 25% of remaining vital capacity ($MEF_{75}$, $MEF_{50}$ and $MEF_{25}$), peak expiratory flow rate (PEF) and forced vital capacity (FVC) were the lung function parameters chosen for assessment from the flow–volume loops. Resistance of the total respiratory system ($R_{tot}$), inspiratory resistance ($R_{in}$), inspiratory vital capacity (VC), residual volume (RV), total lung capacity (TLC), residual volume in per cent of total lung capacity (RV/TLC%) and specific resistance of the respiratory system ($SR_{tot}$) (resistance corrected for lung volume) were used for assessment from the body plethysmograph measurements. Nine subjects were not technically able to perform whole body plethysmography, as they were not able to sit unaided in the pethysmograph. When available, results are given as per cent of predicted values (14).

Scoliosis was assessed as mild, moderate and severe (grade 1, 2 and 3, respectively), after clinical examination and evaluation by an experienced child physiotherapist, and a neuropaediatrician in co-operation with orthopaedic surgeons. Radiological assessment was not performed at the time.

## Assessment of muscular function

Functional status of the children was assessed using Brook's graded scale from 0 to 6 for function of upper limbs and from 0 to 10 for lower limbs: 0 represented best function, and a score of 6 and 10, respectively, represented the poorest muscular function (15).

## Statistical analysis

Demographic data are given as mean with standard deviation (SD) unless otherwise stated. All statistical analyses were performed by use of Statistical Package for Social Sciences (SPSS) version 9.0. Bivariate correlation analyses have been performed employing Pearson's correlation coefficient. Differences between two groups were analysed by *t*-tests, or by ANOVA-test for more than two samples, if data were normally distributed. Otherwise data were analysed by the non-parametric Mann–Whitney *U*-test for two independent samples or by the Kruskall–Wallis ANOVA-test for more than two samples. Differences in categorical variables were compared by the $\chi^2$-test. All tests were performed with two tails and a significance level of 5%.

# RESULTS

Demographic data of the 25 boys with DMD are given in Table 1. The results from lung function measurements are

**Table 1.** Demographic data and muscular function (Brooke) score of the 25 boys with Duchenne's muscular dystrophy. Results are given as mean with standard deviation (SD) in parenthesis and range

| | Mean (SD) | Range |
|---|---|---|
| Age (years) | 12·32 (3·69) | 6–19 |
| Height (cm) | 147·7 (20·7) | 111–183 |
| Weight (kg) | 44·3 (22·5) | 18–99 |
| Muscular function, upper limbs (Brooke score) | 3·84 (1·55) | 1–6 |
| Muscular function, lower limbs (Brooke score) | 7·16 (2·70) | 2–9 |
| Age started walking (months) | 18·0 (5·6) | 11–36 |
| Age stopped walking ($n$=18) (months) | 112·2 (11·7) | 96–132 |

given in Table 2 (maximum expiratory flow–volume loops) and Table 3 (whole body plethysmograph). $FEV_1$, FVC and $FEF_{50}$ were 32·5, 29·3 and 43·8% predicted respectively in the oldest patient requiring (most) nightly ventilator support, whereas lung function values in the further six patients requiring ventilatory support did not differ significantly from the whole group.

The lower limbs had poor muscular function; with a mean score of 7·16, the upper limbs were less affected (mean score 3·84) (Table 1). All parameters of the maximum expiratory flow–volume loop were below predicted values (14), with the lowest mean values recorded for FVC (62·35% of predicted), $FEV_1$ (68·55% of predicted) and $MEF_{75}$ (69·34% of predicted), as shown in Table 2. The parameters thought to represent the function of peripheral airways were higher: $MEF_{50}$ were 77·31% of predicted, whereas $MEF_{25}$ were 88·31% of predicted.

Measured by the whole body plethysmograph, inspiratory VC was found to be 65·61% of predicted value (Table 3), whereas RV was 148·76% of predicted, resulting in TLC of 84·85% of predicted. RV/TLC (%) was 39·24%. ITGV was 97·85% of predicted, whereas inspiratory capacity (IC) was 74·03% of predicted (Table 3). Specific resistance of the airways, $SR_{tot}$, was 1·025.

Lung function parameters dependent upon a maximum inspiratory and expiratory manoeuvres decreased with increasing age. A significant negative correlation was found between $FEV_1$ and age ($r = -0{\cdot}76$, $P < 0{\cdot}001$). By regression analysis it was found that $FEV_1$ in % predicted decreased by 5·61% per year (Fig. 1). FVC also had a significant negative correlation with age ($r = -0{\cdot}70$, $P < 0{\cdot}001$), and FVC in % predicted decreased by 4·2% per year. $MEF_{75}$, $MEF_{50}$ and $MEF_{25}$ in % predicted did not correlate significantly with age. Inspiratory VC in % predicted correlated negatively with age ($r = -0{\cdot}59$,

**Table 2** Lung function measured by maximum expiratory flow volume loops in 25 boys with Duchenne's muscular dystrophy. Values are given as mean (SD) and range

| | Mean (SD) | Range |
|---|---|---|
| FVC (l) | 1·69 (0·47) | 0·86–2·6 |
| FVC % predicted | 62·35 (22·24) | 28·6–123·0 |
| $FEV_1$ ($l\,sec^{-1}$) ($n$=20) | 1·64 (0·39) | 0·88–2·6 |
| $FEV_1$ % predicted ($n$=20) | 68·55 (23·29) | 31·5–113·0 |
| $MEF_{75}$ ($l\,sec^{-1}$) | 3·21 (1·31) | 1·36–6·90 |
| $MEF_{75}$ % predicted | 69·34 (19·67) | 32·8–114·0 |
| $MEF_{50}$ ($l\,sec^{-1}$) | 2·50 (1·04) | 1·02-5·94 |
| $MEF_{50}$ % predicted | 77·31 (25·13) | 37·2–136·0 |
| $MEF_{25}$ ($l\,sec^{-1}$) | 1·41 (0·67) | 0·64–3·15 |
| $MEF_{25}$ % predicted | 88·31 (42·69) | 32·6–203 |
| $MEF_{75-25}$ ($l\,sec^{-1}$) ($n$=20) | 3·21 (1·31) | 1·36–6·90 |
| $FIV_1$ ($l\,sec^{-1}$) $n$=16 | 1·53 (0·33) | 0·92–2·00 |

**Table 3.** Lung function measured by whole body plethysmograph. Only 16 patients succeeded technically in performing all measurements

| | Mean (SD) | Range |
|---|---|---|
| Inspiratory capacity (IC) % predicted | 74·03 (17·78) | 41–106 |
| ITGV% predicted ($n$=18) | 97·85 (30·35) | 62·7–160·0 |
| ITGV (l) ($n$=18) | 1·71 (0·79) | 0·63–3·52 |
| Residual volume (RV) % predicted ($n$=18) | 148·76 (60·84) | 68·8–256·0 |
| RV (l) (n=18) | 1·26 (0·72) | 0·42–2·95 |
| Total lung capacity (TLC) % predicted ($n$=18) | 84·85 (17·61) | 61·3–122·0 |
| TLC (l) (n=18) | 3·04 (1·01) | 1·51–5·62 |
| Vital capacity (inspiratory) (VC) % predicted ($n$=22) | 65·61 (14·53) | 42·– 87·1 |
| VC (l) ($n$=22) | 1·71 (0·50) | 0·77–2·73 |
| RV TLC (%)($n$=18) | 39·24 (11·85) | 17·4–57·4 |
| Specific resistance of the airways ($SR_{tot}$) | 1·025 (0·273) | 0·64–1·63 |

**Table 4.** Lung function in the patients measured twice with an interval of 1 year. The number of patients succeeding technically in measuring the particular lung function parameter is given for each parameter. Lung function is shown as per cent of predicted. Values are given as mean values with 95% confidence intervals in parentheses

| | Measurement 1 | Measurement 2 |
|---|---|---|
| Age (years) | 12·7 (10·6–14·9) | 13·8 (11·6–16·0) |
| FVC, % pred. ($n$=14) | 61·3 (45·5–77·2) | 57·0 (40·8–73·2) |
| $FEV_1$, % pred. ($n$=10) | 70·2 (51·9–88·6) | 65·4 (44·4–86·4) |
| $MEF_{75}$, % pred. ($n$=14) | 63·0 (52·8–73·1) | 65·5 (56·4–74·5) |
| $MEF_{50}$, % pred. ($n$=14) | 69·1 (56·9–81·3) | 67·7 (56·4–79·0) |
| $MEF_{25}$, % pred. ($n$=14) | 74·3 (55·9–92·8) | 71·8 (54·0–89·6) |

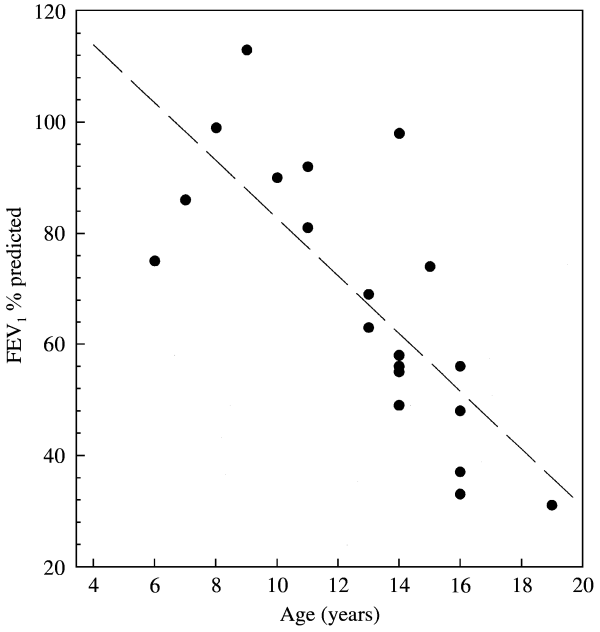


**Fig. 1.** Scatterplot of $FEV_1$ % predicted versus age. $FEV_1$ % predicted demonstrated a significant negative correlation with age ($r = -0{\cdot}76$, $P < 0{\cdot}001$). $FEV_1$% predicted decreased with 5.61% per year.

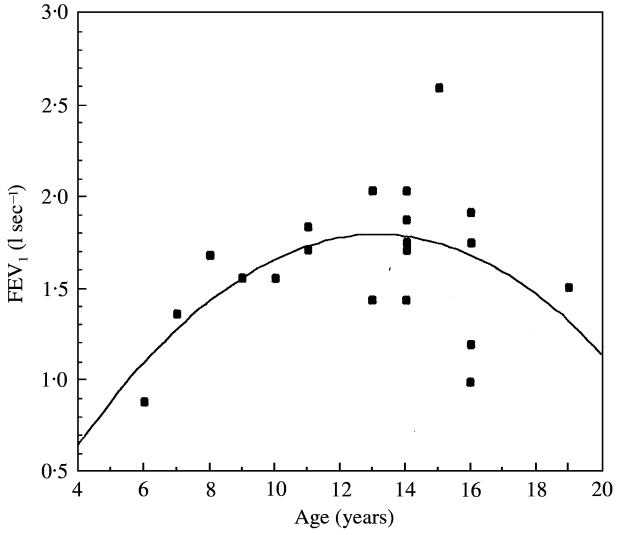


**Fig. 2.** Scatterplot of $FEV_1$ ($l\,sec^{-1}$) versus age.

$P < 0{\cdot}01$), whereas IC did not correlate with age. $SR_{tot}$, ITGV% predicted, RV%TLC, TLC% predicted and RV% predicted did not correlate significantly with age.

$FEV_1$ ($l\,sec^{-1}$) and FVC (litres) increased up to an age of 14 years, thereafter a decrease in absolute values was found, as seen from Fig. 2 for $FEV_1$.

Muscle function score in the upper limbs correlated significantly negatively with $FEV_1$% predicted ($r = -0{\cdot}70$, $P < 0{\cdot}001$), FVC% predicted ($r = -0{\cdot}69$, $P < 0{\cdot}001$), as well as inspiratory VC in % predicted ($r = -0{\cdot}58$, $P - 0{\cdot}01$). $MEF_{75}$, $MEF_{50}$, $MEF_{25}$ in % predicted, $SR_{tot}$, ITGV% predicted, RV%TLC, TLC% predicted and RV% predicted did not correlate significantly with upper limb muscular score. Although to a lesser extent, also lower limb muscular score correlated significantly negatively with $FEV_1$% predicted ($r = -0{\cdot}46$, $P = 0{\cdot}02$), as well as FVC% predicted ($r = -0{\cdot}49$, $P - 0{\cdot}01$). A negative correlation on the border of significance ($r = -0{\cdot}42$, $P = 0{\cdot}06$) was found between inspiratory VC% predicted and lower limb muscle score. The other lung function parameters did not correlate significantly with lower limb muscular function score.

Scoliosis correlated significantly with FVC% predicted and $FEV_1$% predicted ($r = -0{\cdot}54$, $P = 0{\cdot}006$ and $r = -0{\cdot}58$, $P = 0{\cdot}008$, respectively).

In the 14 boys measured twice with an interval of 1 year, all parameters of the maximum expiratory flow–volume loop decreased, but not significantly. Too few of the patients managed to perform whole body plethysmography twice for statistical analyses. Mean difference in IVC and FVC was 0·006 l (0·23 l SD).

## DISCUSSION

Lung function measured by maximum expiratory flow–volume loops was below predicted values for all

parameters. It was found that the parameters decreased with increasing age, and in particular with decreasing muscular function in the upper limbs and lower limbs as assessed by Brooke's score (15). Lung function parameters requiring a maximum inspiratory effort were lower compared to predicted values than lung function measurements not dependent upon a maximum inspiratory effort such as $MEF_{50}$ and $MEF_{25}$ (Table 2).

Whereas $FEV_1$ and FVC corrected for height, weight and age (% predicted) showed a steady decrease throughout the age range, $FEV_1$ and FVC in absolute values increased up to an age of 14 years, thereafter decreasing (Fig. 2 for $FEV_1$). Up to this age, growth seems to some extent to outweigh the reduction observed in $FEV_1$ and FVC corrected for age, height and weight. However, from this age, growth does not compensate for the decline in lung function due to decreasing muscular function. This is in agreement with the observations by Brooke *et al*. (16).

At re-investigation after 1 year, lung function measured by flow–volume loops decreased, but not significantly, in 14 patients, possibly due to the short observation time span.

It has been maintained that patients with neuromuscular diseases demonstrate reductions in flow rates which parallel the decreases in lung volumes (17,18). This is in agreement with our findings for FVC, $FEV_1$ and $MEF_{75}$, but not for $MEF_{25}$ and $MEF_{50}$. It is generally regarded that $MEF_{50}$ and $MEF_{25}$ are sensitive to changes in peripheral airways size, whereas $FEV_1$, $MEF_{75}$, and FVC are thought to reflect the state of the greater, central airways. $FEV_1$ and lung volumes such as FVC and VC depend upon a full inspiration, requiring muscular force to obtain optimal values. This is supported by our findings of a significant correlation between limb muscle function and FVC and $FEV_1$ (Fig. 3). The relationship between FVC and manual muscle test score has previously been described by McDonald *et al*. (1). Griggs maintained that FVC is the most useful pulmonary function test for monitoring disease progression, as it is precise and reproducible, although less sensitive to detect muscle weakness than are maximial inspiratory and expiratory pressures (19). This was also confirmed by Hahn *et al*. who demonstrated that lung volume changes in patients with DMD correlated with respiratory muscle weakness (5). On the other hand, parameters, which are commonly regarded as measures of peripheral airways function (such as $MEF_{25}$ and $MEF_{50}$), may in patients with neuromuscular diseases possibly better reflect the state of the airways and the lungs, taking into consideration the patient's ability to generate sufficient flow through the peripheral airways.

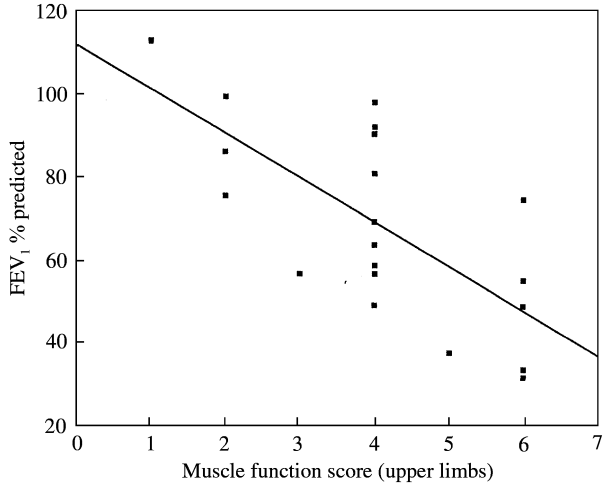


**Fig. 3.** Scatterplot of $FEV_1$ % predicted versus upper limbs muscular function score. The score increased with decreasing muscular function. $FEV_1$% predicted demonstrated a significant negative correlation with upper limbs muscular function score ($r = -0{\cdot}70$, $P < 0{\cdot}001$).

A statistically significant negative correlation was found between lung function ($FEV_1$% predicted) and muscular function score of the upper limbs (Fig. 3), whereas this was not found for the lower limbs. This may be due to the close anatomical relationship between the muscles of the upper limbs and the respiratory muscles, as the muscles of the lower limbs are more severely affected at an early stage of the disease than the muscles of the upper limbs and the trunk. There was also a significant inverse relationship between clinical grading of scolisis and lung function in per cent predicted, in the present study. There are conflicting data on the effect of spinal stabilisation and pulmonary function. Galasko demonstrated that spinal stabilization reduced the annual decline of lung function in patients with DMD (20). On the other hand, Miller found no difference in the rate of deterioration of the percentage of normal FVC after spinal fusion in a group of 21 children compared to 46 non-fused DMD sufferers (21). Kennedy in a later study found that spinal stabilization in DMD did not alter the decline in pulmonary function, nor did it improve survival (22). Spinal surgery was refused by the subjects in the present study, thus no such assessment could be performed.

The decline in $FEV_1$ and FVC (% predicted) with age (Fig. 1) and the lack of correlation between $MEF_{50}$ and $MEF_{25}$ (% predicted) and age is a further support that the former parameters more closely reflect the decline in muscular function.

The mean difference between inspiratory and expiratory forced capacity was very small (0·006 l), suggesting that the subjects had sufficient muscular strength to empty their lungs during forced expiratory manouvre, thus justifying the interpretation of peripheral lung function values.

In conclusion, we found that lung function measured in boys with DMD by flow–volume loops and whole body plethysmography decreased with increasing age and

particularly FVC and $FEV_1$ in % predicted values reflected the muscle function of the upper limbs.

Measurements of flow volume loops may be of particular value in the clinical follow-up of patients with DMD as they may assist in the evaluation of both the assessment of muscular function as well as the state of the respiratory tract.

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