Changes in Spirometry Over Time as a Prognostic Marker in Patients with Duchenne Muscular Dystrophy

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Duchenne muscular dystrophy (DMD) causes a progressive impairment of muscle function leading to hypercapnic respiratory failure. Most studies of respiratory function in DMD have been cross-sectional rather than longitudinal, and these data have not been related to survival. We retrospectively studied 58 patients with DMD with at least 2 yr of follow-up spirometry and known vital status. Spirometry was abnormal at entry: median FEV₁, 1.60 L (range 0.4 to 2.6 L), FVC 1.65 L (range 0.45 to 2.75 L), FVC 64% predicted (range 29 to 97%). Individual rates of change of vital capacity varied, with a median annual change of −0.18 L (range 0.04 to −0.74 L), −0.80% predicted FVC (range 2 to −39%). During the study 37 patients died; the median age of death, calculated by Kaplan–Meier analysis, was 21.5 yr (range 15 to 28.5 yr). The age when vital capacity fell below 1 L was a strong marker of subsequent mortality (5-yr survival 8%). The maximal vital capacity recorded and its rate of decline (however expressed) predicted survival time. Repeated spirometric measurement provides a simple and relatively powerful means of assessing disease progression in these patients and should be considered when planning treatment trials.

Keywords: Duchenne muscular dystrophy; spirometry; pulmonary function; survival

Duchenne muscular dystrophy (DMD) is a progressive sex-linked disorder characterized by the production of abnormal dystrophin (1), a 427 kD protein, and leading to progressive impairment of muscle strength and structure. The majority of affected boys die from respiratory failure (2) but the time to death is variable. Respiratory function has been studied repeatedly, and a characteristic pattern of restrictive spirometry and reductions in maximal respiratory pressures has been reported (2–11). Estimates of the mean change in these variables with time suggest that vital capacity and respiratory muscle strength decline monotonically in a predictable fashion (2, 3–5, 7–11). However, the age distribution of patients reaching a specified vital capacity, for example, less than 1 L, is not normal (6), raising the possibility of individual variation in decline of lung function. Moreover, death from respiratory causes was commonest in those with the worst pulmonary function (3, 6).

Studies reporting individual rates of change in lung function have not been presented, although two groups have reported mean changes in the evolution of vital capacity for specific age groups (3, 8). To date, no study has related changes in vital capacity to subsequent prognosis. For the past 15 yr spirometry has been recorded routinely in patients with DMD attending our center. Using these data, we have examined the evolution of spirometric abnormality in patients with well-characterized DMD and related these changes to subsequent progress. We hypothesized that the rate of change of vital capacity would predict respiratory mortality and that the time to a specified level of ventilatory impairment would be prognostically useful. Although other measurements such as recording of respiratory muscle pressures have been made during follow-up, we have much more complete data on spirometry, which is the focus of this report.

METHODS

Records from all patients 10 yr of age or older who attended for at least 2 yr from 1986 to 1999 was analyzed. The diagnosis of DMD was based on the presence of a characteristic clinical and family history, together with a combination of electromyogram (EMG), muscle biopsy, and latterly molecular genetic data. All patients were nonsmokers and none received medication likely to influence lung function measurements. The timing of spinal surgery, the age at which the patient stopped walking, the presence of symptomatic cardiac complications, and the use of noninvasive positive pressure ventilation (NIPPV) was recorded. Vital status was established by obtaining hospital records for evidence of current clinic review after the study or confirmation of the date and cause of death. Ascertainment was complete for all eligible participants. Data collection was approved by our institutional ethical committee.

Measurements

Spirometry, height or arm span, and weight were recorded at each clinic visit. The frequency of visits varied depending on the clinician’s assessment of the patient’s FEV₁ and FVC. FVC was measured with the patient seated using a dry bellows spirometer (Vitalograph; Beckenham, Kent, UK) until 1995 and thereafter using a hand-held electronic turbine spirometer (MicroMedical). The spirometer mouthpiece was supported in the mouth if the patient could not do so himself. The highest values from three recordings meeting American Thoracic Society (ATS) criteria for FEV₁ and FVC measurement (12) were used, and predicted FVC was calculated (13). An approximation of height was obtained from the arm span for all measurements, with each arm segment being measured separately in patients with contractures (14). Weight was measured in a calibrated weighing chair, and body mass index (BMI) was calculated as weight (kg)/arm span(m)².

Statistics

Data were analyzed using parametric or nonparametric methods, depending on the distribution of the variables using SPSS for Windows version 9.0. Population variables were expressed as mean (standard deviation) or median (range), and association between variables assessed using Spearman rank correlation coefficients. Decline in FVC was calculated from the time of maximal FVC (or oldest age at maximal FVC if the same on two or more occasions) to the last recording. The division of the population into three groups according to maximal FVC (maximal FVC < 1.2 L, 1.2 to 1.7 L, and > 1.7 L) followed the approach of Rideau and coworkers (5), but without allowing for the age the patient stopped walking. Comparison of groups was by Student’s t test for two groups, and one-way analysis of variance (ANOVA) for three or more. Survival analysis used Kaplan–Meier plots and Cox regression analysis.
TABLE 1. AGE STOPPED WALKING, MAXIMAL WEIGHT AND HEIGHT, INITIAL FEV₁, FVC, FEV₁/FVC, AND AGE OF FIRST RECORDING*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean/Median</th>
<th>Standard Deviation/Range</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age stopped walking, yr</td>
<td>10.5</td>
<td>8.0–15.0</td>
<td>45</td>
</tr>
<tr>
<td>Maximal span, m</td>
<td>1.68</td>
<td>0.12</td>
<td>55</td>
</tr>
<tr>
<td>Maximal BMI, kgm²</td>
<td>17.0</td>
<td>11.1–30.3</td>
<td>55</td>
</tr>
<tr>
<td>First recorded FEV₁, L</td>
<td>1.60</td>
<td>0.4–2.6</td>
<td>46</td>
</tr>
<tr>
<td>First recorded FVC, L</td>
<td>1.65</td>
<td>0.45–2.75</td>
<td>58</td>
</tr>
<tr>
<td>First recorded FVC, % pred</td>
<td>64%</td>
<td>29–97%</td>
<td>58</td>
</tr>
<tr>
<td>First FEV₁/FVC</td>
<td>0.95</td>
<td>0.67–1.0</td>
<td>49</td>
</tr>
<tr>
<td>Age of first recording, yr</td>
<td>12.0</td>
<td>10–18</td>
<td>58</td>
</tr>
</tbody>
</table>

* Results are given as mean and standard deviation or median and range according to distribution.

RESULTS

Patient Characteristics and Baseline Data

Important clinical milestones and the baseline spirometric characteristics are presented in Table 1. Fifty-eight patients met our entry criteria with a median follow-up of 7.2 (range 2 to 16.3) yr. Vital capacity data was available from a median age of 12.0 (range 10 to 18) yr. The median age at which patients stopped walking was 10.5 (range 8 to 15) yr, but not recorded in 13 patients. Luque spinal instrumentation was performed in 26 patients; a further 16 patients had a scoliosis but declined or were unfit for surgery. Group mean FVC did not differ between recordings with the bellows or turbine spirometer (mean FVC 1.86 L pre; mean FVC 1.76 L post; not significant). All spirometric variables were reduced at study onset, and a restrictive impairment was seen which persisted throughout subsequent measurements.

Changes in Vital Capacity with Time

A total of 523 FVC recordings (median 8.5/patient, range 2 to 16) were made. The variable pattern of change of FVC is shown for individual patients in Figure 1. To view these patterns more easily, the cohort was arbitrarily separated into four groups by age of death (Figures 1A–1C) and into those still alive (Figure 1D). FVC showed a variable but progressive fall, the median rate of decline was 0.18 (range from 0.04 to 0.74) L/year. This corresponded to −8.0 (range 2 to 39) % predicted/year. For the whole group, median FVC at age 14 was 1.8 L (range 0.55 to 3.5, n = 34) and at 18 was 1.4 L (range 0.4 to 3.7, n = 21). The corresponding mean percentage of predicted values were 50% (21 to 87%) at age 14 and 36% (11 to 75%) at age 18.

The median age at which the FVC reached 1 L was 17 (range 13 to 25.5) yr. The age when FVC reached 25% predicted was similar, with a median value of 17.75 yr (range 13.5 to 23) years.

Survival Experience

During the study, 37 patients died. The median survival calculated by Kaplan–Meier analysis was 21.5 (range 15 to 28.5) yr. The populations’ survival experience is shown in Figure 2A and the distribution of age of death is shown in Figure 2B. Four patients who died were known to have congestive cardiac failure. They died at 16, 17, 19, and 22.5 yr, their last vital capacities before death being 0.75 L, 2.30 L, 2.69 L, and 0.5 L respectively. The median age of death during follow-up was 20.5 yr.

Prognosis

Table 2 contrasts a number of variables that might predict mortality, split by the median age of death for this group. The age at which FVC reached 1 L was significantly lower in those dying soonest. To determine whether any other factor predicted mortality, the remaining variables in Table 2 were entered into a Cox regression analysis. Only the change in percentage of predicted FVC per year (p < 0.0003) and maximal FVC were predictive of survival (p < 0.0005). This latter term could be substituted by maximal height with almost equal explanatory power.

* Results are given as mean and standard deviation or median and range according to distribution.

Figure 1. Change in vital capacity for each individual. (A) Group consisting of individuals who died at age 19 yr or younger. (B) Group whose members died between 20 and 21.9 yr of age. (C) Group comprised of patients who died at age 22 yr or older. (D) Group still alive.
that patients with an FEV\textsubscript{1} of 3.1 yr with a 5-yr survival of 8% (Figure 4). Kaplan–Meier analysis; the population median survival was 20.5 yr. This may reflect the referral pattern to our center, so the timing of our measurements was not uniformly spaced, nor were all the patients referred at the same age. The overall survival of our patients was better than anticipated, with a median age at death of 20.5 yr. This may reflect the referral pattern to our center, so the timing of our measurements was not uniformly spaced, nor were all the patients referred at the same age. The overall survival of our patients was better than anticipated, with a median age at death of 20.5 yr. This may reflect the referral pattern to our center, so the timing of our measurements was not uniformly spaced, nor were all the patients referred at the same age. The present data reflect the natural history of patients with DMD managed without ventilatory support. Recent data suggest that the FEV\textsubscript{1} continues to decline during NIPPV treatment despite normalization of the blood gas tensions (15). We have not included data from patients treated with NIPPV in case this affected the FVC, our primary outcome measure. Although echocardiography can detect occult cardiac disease (7), this was not routinely performed during the follow-up in these patients. The clear relationship between declining respiratory function and deaths from respiratory causes gives us confidence that the clinical diagnosis in those who died was accurate. Our patients were nonsmokers, which eliminates one variable known to influence the rate of lung function development in teenagers (16).

This is the largest serial spirometry data set to date in this condition, with 523 observations in 58 patients compared with 238 observations in 80 patients in the only other reported series (3). The group mean decline in FVC of 8.0% predicted per year is in good agreement with other large series (3, 8). We attempted to define a plateau phase of lung function, as suggested by others, but the limitations of using an arbitrary criterion for between-test reproducibility made this impractical.

The overall survival of our patients was better than anticipated, with a median age at death of 20.5 yr. This may reflect the referral pattern to our center, so the timing of our measurements was not uniformly spaced, nor were all the patients referred at the same age. The present data reflect the natural history of patients with DMD managed without ventilatory support. Recent data suggest

In this series only three patients died before their FVC fell to 1 L, and this variable was highly correlated with age of death (r = 0.94, n = 37, p < 0.0001) (Figure 3). The solid circles in Figure 3 indicate those individuals still alive with an FVC of < 1 L, and they lie to the left of the line of identity. Survival when the FVC fell below 1 L was investigated using Kaplan–Meier analysis; the population median survival was 3.1 yr with a 5-yr survival of 8% (Figure 4).

Separation into groups using the Rideau criteria confirmed that patients with an FEV\textsubscript{1} > 1.7 L survived significantly longer (p < 0.0001), but these data were strongly influenced by a small number of patients with very low maximal FVC who died early.

**DISCUSSION**

Abnormal respiratory function is present in DMD almost as soon as it can be measured reliably, from around age 8 onward, and this was true of our patients. Although measurements of maximal respiratory pressures give a direct assessment of global respiratory muscle function (8) and may point to the development of early problems with cough and reduced secretion clearance (3), most clinics rely on measurements based on spirometry and in particular FVC. This reflects the availability of relatively inexpensive portable equipment and the direct relevance of these measurements to the development of further respiratory complications (3, 6). Using this simple assessment, we were able to document a significant variability between individuals in the evolution of their pulmonary function that would not have been suspected had our data been pooled.

Our patient population reflects the referral pattern to our center, so the timing of our measurements was not uniformly spaced, nor were all the patients referred at the same age. The present data reflect the natural history of patients with DMD managed without ventilatory support. Recent data suggest
in the proportional hazard model and was significantly less in patients dying after the age of 21 yr than those dying sooner. We cannot exclude a cardiac contribution to our patient’s death, but this does not diminish the utility of pulmonary function measurements, which also predict death from cardiac disease in the general population (17). Other physiologic abnormalities, such as sleep-related breathing disorders, particularly during rapid eye movement (REM) sleep, may be important in causing death (18). However, we have previously shown that the severity of these problems as assessed by the minimal nocturnal oxygen saturation was closely related to FVC (19).

The heterogeneity of decline in pulmonary function was reflected by the variable age at which the FVC fell below 1 L. Our data confirmed previous suggestions that stratification by maximal FVC value can give prognostic information (5), but emphasize that the age at which the FVC becomes < 1 L is a reliable milestone, indicating a high chance of death in the next 3 yr. This has practical significance and may explain the disappointingly negative results of a previous randomized trial of NIPPV in DMD where patients entered with a vital capacity of approximately 2 L (20). The follow-up period of this trial may have been insufficient to allow any beneficial effect to emerge. Clinically, we now use this threshold as an important indicator for discussing future disease management with patients and their caretakers, considering polysomnography and other more complex investigations, and discussing issues related to the need for future ventilatory support.

In summary, serial measurements of FVC provide a simple and reliable means of assessing disease progression in Duchenne muscular dystrophy. The age at which this value falls below 1 L is an appropriate point at which to consider more intensive patient support. Whether other treatment interventions such as physiotherapy will modify the progression of lung function decline is still to be determined, but individual variation in the rate of decline of FVC is an important variable to be considered when evaluating any intervention strategy.

References