Characterization of pulmonary function in 10–18 year old patients with Duchenne muscular dystrophy

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Abstract

Pulmonary function loss in patients with Duchenne muscular dystrophy (DMD) is progressive and leads to pulmonary insufficiency. The purpose of this study in 10–18 year old patients with DMD is the assessment of the inter-correlation between pulmonary function tests (PFTs), their reliability and the association with the general disease stage measured by the Brooke score. Dynamic PFTs (peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory volume in one second [FEV1]) and maximum static airway pressures (MIP, MEP) were prospectively collected from 64 DMD patients enrolled in the DELOS trial (ClinicalTrials.gov, number NCT01027884). Baseline PEF percent predicted (PEF%p) was <80% and patients had stopped taking glucocorticoids at least 12 months prior to study start. At baseline PEF%p, FVC%p and FEV1%p correlated well with each other (Spearman's rho: PEF%p–FVC%p: 0.54; PEF%p–FEV1%p: 0.72; FVC%p–FEV1%p: 0.91). MIP%p and MEP%p correlated well with one another (MIP%p–MEP%p: 0.71) but less well with PEF%p (MIP%p–PEF%p: 0.40; MEP%p–PEF%p: 0.41) and slightly better with FVC%p (MIP%p–FVC%p: 0.59; MEP%p–FVC%p: 0.74). The within-subject coefficients of variation (CV) for successive measures were 6.97% for PEF%p, 6.69% for FVC%p and 11.11% for FEV1%p, indicating that these parameters could be more reliably assessed compared to maximum static airway pressures (CV for MIP%p: 18.00%; MEP%p: 15.73%). Yearly rates of PFT decline (placebo group) were larger in dynamic parameters (PEF%p: −8.9% [SD 2.0]; FVC%p: −8.7% [SD 1.1]; FEV1%p: −10.2% [SD 2.0]) than static airway pressures (MIP%p: −4.5 [SD 1.3]; MEP%p: −2.8 [SD 1.1]). A considerable drop in dynamic pulmonary function parameters was associated with loss of upper limb function (transition from Brooke score category 4 to category 5). In conclusion, these findings expand the understanding of the reliability, correlation and evolution of different pulmonary function measures in DMD patients who are in the pulmonary function decline phase.
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Keywords: Duchenne muscular dystrophy; pulmonary function; forced vital capacity; peak expiratory flow

1. Introduction

Duchenne muscular dystrophy (DMD), the most common and severe form of muscular dystrophy, is characterized by progressive respiratory muscle weakness which causes restrictive respiratory disease, impaired clearance of airway secretions, recurrent pulmonary infections due to ineffective cough, hypoventilation and eventually respiratory failure [1–4]. Routine use of glucocorticoids (GCs), the introduction of mechanical insufflation–exsufflation devices to improve airway

clearance and non-invasive ventilation to ameliorate alveolar hypoventilation have become standard of care, which together have increased the average life expectancy in DMD patients [5–9]. Interestingly, a study of all-cause mortality showed that the number of deaths due to respiratory failure was not significantly influenced by the GC use status of patients [10].

Serial assessment of pulmonary function is a critical element of recommended routine monitoring for patients with DMD, as it may enable early identification and treatment of pulmonary complications [11,12]. According to standard of care recommendations [13] spirometry is required every 6 months, recording dynamic pulmonary function parameters such as forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF), a measure of

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expiratory muscle strength in patients without airway obstruction [14]. Maximum static airway pressures (maximal inspiratory pressure [MIP] and maximal expiratory pressure [MEP]) are also measured frequently, particularly in early stages of the disease.

Although the assessment of pulmonary function decline in DMD is important in routine patient care, there is still limited knowledge about the correlation between these pulmonary function parameters, their reliability and sensitivity to change over time. Recent natural history data were reported in order to better understand the influence of age, glucocorticoid use and disease status on pulmonary function evolution in DMD. Emerging evidence from these data indicates that in patients with DMD (i) PEF and FVC expressed as percent of predicted (PEF%p, FVC%p) are well correlated [15], (ii) GC use delays the onset of pulmonary function loss, but once established, the rate of decline is comparable between GC-users and patients who are currently not using GCs [16–18], (iii) loss of FVC, FEV1 and PEF expressed as percent predicted follow a linear rate of decline from ~80% to ~30% [15,18,19] and (iv) the time of loss of ambulation is a predictor of pulmonary function loss [19]. Moreover, FVC%p, FEV1%p and PEF%p appear to follow a more predictable and reliable change with age than maximum static airway pressures (MIP%p, MEP%p) and peak cough flow (PCF) [15,16].

Here we report pulmonary function data from a well-defined DMD patient cohort (not using concomitant GC) prospectively enrolled in a randomized, placebo-controlled, phase 3 clinical trial (DELOS, Duchenne muscular dystrophy long-term idebenone study) which demonstrated that idebenone, a short-chain benzoquinone, significantly reduced the loss of pulmonary function over the 52-week study period [20–22]. We have now further analyzed cross sectional (baseline) data from all trial participants and longitudinal data from the placebo group of DELOS to determine the correlation between dynamic and static pulmonary function outcomes, their inter-correlation as well as correlation to upper limb function and the annual rate of change with the goal to provide a comprehensive characterization of pulmonary function in 10–18 year old patients with DMD who are not taking concomitant GCs and further expand our understanding of the natural course of pulmonary disease in DMD.

2. Patients and methods

2.1. Prospective data collection

Pulmonary function data were obtained from patients participating in DELOS, a prospectively planned, multi-center, phase 3 clinical trial evaluating the efficacy of idebenone 900 mg/day (Raxone®, Santhera Pharmaceuticals, Switzerland) compared to placebo [20]. Patients were enrolled between July 2009 and December 2012 in study centers located in Belgium, Germany, the Netherlands, Switzerland, France, Sweden, Austria, Italy, Spain and the USA. The trial and any changes to the protocol were approved by relevant national authorities and the institutional review boards or independent ethics committees in the countries of the participating centers and conducted in accordance with good clinical practice and the principles of the Declaration of Helsinki. Prior to any study-related procedure, written informed consent was obtained from all patients and/or parents or guardian. This study is registered with ClinicalTrials.gov, number NCT01027884, and the overall outcome was reported previously [20–22].

2.2. Patients

Patients aged 10–18 years with a documented and confirmed diagnosis of DMD were eligible for enrollment. Study participants had to have stopped taking glucocorticoids (GC) at least 12 months prior to enrollment and were not allowed to take GC during the 52-week study period. Furthermore, only patients who had reached the stage of pulmonary function decline, defined as PEF%p < 80% were enrolled. Based on their PEF%p at baseline, study participants were stratified into two subgroups (PEF%p <40% and 40–80%). Exclusion criteria included: (i) dependence on assisted ventilation (non-invasive nocturnal, daytime non-invasive or continuous invasive), (ii) documented DMD-related hypoventilation for which assisted ventilation is needed according to current standard of care guidelines (e.g. FVC%p < 30%) and (iii) inability to form a mouth seal to allow precise assessment of pulmonary function and mouth pressures. Patients with symptomatic heart failure (high probability of death within one year of baseline) and/or symptomatic ventricular arrhythmias were also excluded from the study. There were no selection criteria for ambulatory status or for any dystrophin mutation type. The intent-to-treat (ITT) population consisted of 64 patients; 33 patients were randomized to the placebo group.

2.3. Pulmonary function tests

Pulmonary function tests (PFT) were performed during hospital visits at screening, at baseline (within 6 weeks from screening) and at weeks 13, 26, 39 and 52. FVC, FEV1 and PEF were assessed using a Pneumotrac Spirometer 6800 (Vitalograph, UK). MIP and MEP were measured with a MicroRPM instrument (Medical Supply Store, Chorley, UK). All PFTs were performed with the aid of a qualified, trained and certified operator and in accordance with the American Thoracic Society/European Respiratory Society guidelines [23]. At each study visit the PFTs were to be carried out in the following sequence: PEF, FVC (which included FEV1), MIP and MEP. For each pulmonary function parameter, the highest value from a minimum of three and up to five consecutive maneuvers was used for analysis. All PFT parameters were normalized for height (derived from ulnar length [24,25]), weight, age and race using established conversion equations as shown in Supplementary material Table S1.

2.4. General disease status

The general disease status of patients was determined by their ambulatory status and upper limb function. For this, patients were counted as non-ambulatory if they were a non-ambulant wheelchair user at baseline. Upper limb function was assessed by the Brooke Upper Extremity scale [26], a 6-item scale where a higher score indicates a more severe functional impairment of the upper limbs (Supplementary material Fig. S1).

2.5. Statistical analysis

Patient demographics were analyzed using descriptive statistics (expressed as mean and standard deviation [SD]). Yearly 'rates of change' of pulmonary function parameters for the patients randomized to the placebo group of the study were calculated as change from baseline to week 52 using a mixed model for repeated measures (MMRM) with 'visit' as a fixed factor in the model and 'baseline assessment' as a covariate using SAS 9.3 (SAS Institute Inc., Cary, North Carolina, USA). Data were presented as estimated mean change with standard errors and 95% confidence intervals (CI); *p*-values indicate whether the yearly change was significant. Within subject coefficient of variation (CV) was calculated for assessments conducted at screening and at baseline which were ≤6 weeks apart. CV data and correlations between pulmonary function parameters at baseline expressed as Spearman's rho were calculated using the software package R [27].

3. Results

3.1. Patient characteristics and general disease status

Patient characteristics at baseline for the ITT population and for the placebo group are summarized in Table 1. The average age of the ITT population was 14.3 years and patients were either GC-naive (43.8%) or had used GC previously (56.3%) but on average stopped their use 3.7 years prior to study enrollment. Participating patients were already in an advanced disease stage as seen in the high proportion of non-ambulant patients (92.2%) and the overall high Brooke score of 4.2

points. Only 7 of 64 patients (10.9%) had a Brooke score of 1 or 2, but 38 of 64 (59.4%) patients had already reached a Brooke score of 5 or 6 (Table 1) which implicates that patients could no longer raise their hands to their mouth (Supplementary material Fig. S1). The baseline characteristics of the placebo subgroup and the subgroups of patients separated by previous GC use status were generally comparable to the ITT population. Interestingly, the subgroup of prior GC-users was not different from GC-naive patients with respect to general disease severity measured as proportion of non-ambulant patients and Brooke upper extremity function score. When patients were divided by the median age of the ITT population (14 years) and the younger and older subgroups compared, it became apparent that patients ≤14 years of age were less advanced in their disease stage, seen in a smaller proportion of non-ambulant patients (87.5%) and a lower average Brooke score (3.8) compared to the subgroup of patients >14 years (96.9% of non-ambulant patients; Brooke score: 4.6).

3.2. Analysis of pulmonary function status

The vast majority of patients (81.3%) had PEF%p 40–80% and only a small proportion (18.8%) had already very advanced pulmonary function loss with PEF%p < 40% at baseline (Table 2). A similar distribution between PEF%p strata at baseline were seen for the placebo group, the subgroup of non-ambulant patients and for patients irrespective of their prior GC use status. Only when patients were separated by age, a difference became apparent with more patients in the >14 year

Table 1
Baseline characteristics and general disease status.

Patient characteristics at baseline	Patient population		GC use status (prior GC-use)		Ambulatory status	Age category (by median)	
	ITT (N = 64)	Placebo (N = 33)	No (N = 28)	Yes (N = 36)	Non ambulant (N = 59)	≤14 y (N = 32)	>14 y (N=32)
Age, years mean (SD)	14.3 (2.7)	15.0 (2.5)	14.5 (2.9)	14.1 (2.5)	14.5 (2.6)	12.0 (1.2)	16.6 (1.5)
Weight (kg) mean (SD)	58.7 (18.3)	61.9 (18.0)	59.5 (22.7)	58.1 (14.3)	60.4 (17.8)	51.1 (13.7)	66.4 (19.3)
Height (cm)* mean (SD)	160.0 (12.0)	162.4 (12.4)	160.8 (13.7)	159.3 (10.7)	160.9 (11.7)	151.5 (9.4)	168.5 (7.6)
Non-ambulatory N (%)	59 (92.2%)	31 (93.9%)	25 (89.3%)	34 (94.4%)	59 (100%)	28 (87.5%)	31 (96.9%)
Prior GC use N (%)							
No	28 (43.8%)	14 (42.4%)	28 (100.0%)	0 (0%)	25 (42.4%)	13 (40.6%)	15 (46.9%)
Yes	36 (56.3%)	19 (57.6%)	0 (0%)	36 (100.0%)	34 (57.6%)	19 (59.4%)	17 (53.1%)
Time since last GC use (years) mean (SD)	3.7 (2.1)	4.3 (2.2)	n.a.	3.7 (2.1)	3.6 (2.2)	3.0 (1.7)	4.4 (2.3)
Brooke score (N, %)							
Score = 1	2 (3.1%)	0 (0.0%)	1 (3.6%)	1 (2.8%)	0 (0.0%)	2 (6.3%)	0 (0.0%)
Score = 2	5 (7.8%)	1 (3.0%)	2 (7.1%)	3 (8.3%)	3 (5.1%)	4 (12.5%)	1 (3.1%)
Score = 3	9 (14.1%)	4 (12.1%)	3 (10.7%)	6 (16.7%)	8 (13.6%)	6 (18.8%)	3 (9.4%)
Score = 4	10 (15.6%)	7 (21.2%)	6 (21.4%)	4 (11.1%)	10 (16.9%)	6 (18.8%)	4 (12.5%)
Score = 5	37 (57.8%)	21 (63.6%)	15 (53.6%)	22 (61.1%)	37 (62.7%)	14 (43.8%)	23 (71.9%)
Score = 6	1 (1.6%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (3.1%)
Mean (SD)	4.2 (1.2)	4.5 (0.8)	4.3 (1.2)	4.2 (1.2)	4.4 (0.9)	3.8 (1.3)	4.6 (0.8)

Data are means (SD) from descriptive statistics.
* Derived from ulnar length according to Gauld et al. (2003); Gauld et al. (2004).

Table 2
Pulmonary function status at baseline.

Patient characteristics at baseline	Patient population		GC use status (prior GC-use)		Ambulatory status	Age category (by median)	
	ITT (N = 64)	Placebo (N = 33)	No (N = 28)	Yes (N = 36)	Non ambulant (N = 59)	≤14 y (N = 32)	>14 y (N=32)
PEF %p strata							
PEF 40%–80%	52 (81.3%)	26 (78.8%)	23 (82.1%)	29 (80.6%)	47 (79.7%)	29 (90.6%)	23 (71.9%)
PEF < 40%	12 (18.8%)	7 (21.2%)	5 (17.9%)	7 (19.4%)	12 (20.3%)	3 (9.4%)	9 (28.1%)
Baseline PFT							
PEF [L/min]	226.0 (54.7)	233.8 (59.6)	232.9 (51.8)	220.6 (57.0)	225.7 (55.7)	212.3 (45.3)	239.6 (60.3)
PEF%p	53.8 (11.8)	54.2 (13.2)	55.2 (10.9)	52.8 (12.5)	53.1 (12.0)	56.5 (10.9)	51.2 (12.2)
FVC [L]	1.9 (0.5)	1.9 (0.5)	1.8 (0.5)	1.9 (0.5)	1.9 (0.5)	1.9 (0.4)	1.8 (0.6)
FVC%p	52.8 (18.1)	50.4 (20.0)	51.5 (19.1)	53.8 (17.5)	51.6 (18.0)	64.5 (15.0)	41.1 (12.7)
FEV1 [L]	1.6 (0.5)	1.6 (0.5)	1.6 (0.4)	1.6 (0.5)	1.6 (0.5)	1.6 (0.4)	1.5 (0.6)
FEV1%p	51.4 (18.5)	49.5 (20.6)	52.0 (18.9)	51.0 (18.4)	49.9 (18.2)	62.4 (15.5)	40.5 (14.5)
Tiffeneau index	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)
MIP	45.9 (20.8)	44.6 (16.9)	45.1 (15.2)	46.6 (24.4)	46.8 (20.8)	47.4 (20)	44.5 (21.7)
MIP %p	41 (19.6)	38.5 (16.9)	40.0 (15.4)	41.7 (22.6)	41.2 (19.6)	47.4 (19.8)	34.5 (17.5)
MEP	40.1 (16.0)	39.7 (16.6)	34.7 (11.6)	44.4 (17.8)	39.8 (16.4)	42.6 (14.5)	37.7 (17.3)
MEP %p	26.6 (12.2)	25.1 (12.2)	22.8 (9.4)	29.7 (13.3)	25.9 (12.2)	32.5 (11.4)	20.8 (10.1)

Data are means (SD) from descriptive statistics. For convenience, data for MIP and MIP%p are also presented as positive values. The Tiffeneau Index is calculated as FEV1/FVC.

subgroup (28.1%) having PEF%p below 40% at baseline compared to the subgroup of patients ≤14 years (9.4%).

Average baseline pulmonary function data of dynamic flow- (PEF%p) and volume-related parameters (FVC%p; FEV1%p) were comparable between the ITT population, the subgroup of non-ambulant patients, the GC-naive patients and the subgroup of patients who previously used GC. Only MEP and MEP%p were significantly higher in the previous GC-user group compared to patients who never used GC (statistical test for difference according to GC use status: MEP: $p = 0.011$; MEP%: $p = 0.018$). The subgroup of younger patients (≤14 years) generally had higher PFT values indicating a better pulmonary function status compared to patients in the older (>14 years) subgroup (statistical test for difference between age categories for percent predicted PFTs: PEF%p: $p = 0.068$; FVC%p: $p < 0.0001$; FEV1%p: $p < 0.0001$; MIP%p: $p = 0.007$; MEP%p: $p < 0.0001$). The Tiffeneau index calculated as the ratio of FEV1/FVC and a measure of airway obstruction was in the normal range in all populations studied indicating the restrictive and not obstructive nature of pulmonary function loss in DMD patients. Following a recent proposal for the use of modified ATS criteria in DMD patients [18], we assessed how many patients had differences of >10% between the highest two FVC values (measured in liters) at baseline. There were 6 patients (all randomized to the idebenone group) who had >10% difference between their highest two FVC values at baseline (mean difference: 14.9%; SD: 4.3%). The mean difference between the highest two FVC values at baseline was 3.8% (SD 4.5%) for the ITT population and 2.7% (SD: 2.4%) when the 6 patients with differences of >10% between the two highest FVC values were excluded from the ITT population.

3.3. Correlation of pulmonary function parameters and reliability of their assessment

At baseline, dynamic flow- (PEF%p) and volume-related (FVC%p, FEV1%p) pulmonary function outcomes correlated well with one another (Fig. 1) as reflected by their good inter-correlation using Spearman's rho coefficients: PEF%p– FVC%p: 0.54; PEF%p–FEV1%p: 0.72; FEV1%p–FVC%p: 0.91. Not surprisingly, the strongest correlation was observed between FVC%p and FEV1%p, both representing volume-related pulmonary function outcomes. Maximum static airway pressures (MIP%p; MEP%p) correlated well with one another at baseline (MIP%p–MEP%p: 0.71) but less well with the flow-related parameter (MIP%p–PEF%p: 0.40; MEP%p–PEF%p: 0.41) and slightly better with the volume-related parameter (MIP%p–FVC%p: 0.59; MEP%p–FVC%p: 0.74). The good inter-correlation between PEF%p, FVC%p and FEV1%p was confirmed for the change from baseline to week 52 in the placebo group (Spearman's rho coefficients: PEF%p–FVC%p: 0.60; PEF%p–FEV1%p: 0.79; FEV1%p–FVC%p: 0.73).

The within-subject coefficient of variation (CV) was assessed between the screening and baseline visits, which took place on an average of 16.7 days (SD 12.4) apart. The resulting CVs from screening to baseline measures indicated that the most reliably assessed pulmonary function outcomes were FVC%p (CV: 6.69%) and PEF%p (CV: 6.97%) followed by FEV1%p (CV: 11.11%) (Table 3). In contrast, CVs for maximum static airway pressures were considerably higher (MIP%p: 18.0%; MEP%p: 15.4%) indicating patients' difficulties to reliably reproduce these measures. CVs were also analyzed for the subgroups of patients ≤14 or >14 years of age

Table 3
Within-subject coefficients of variation (CV) from screening to baseline.

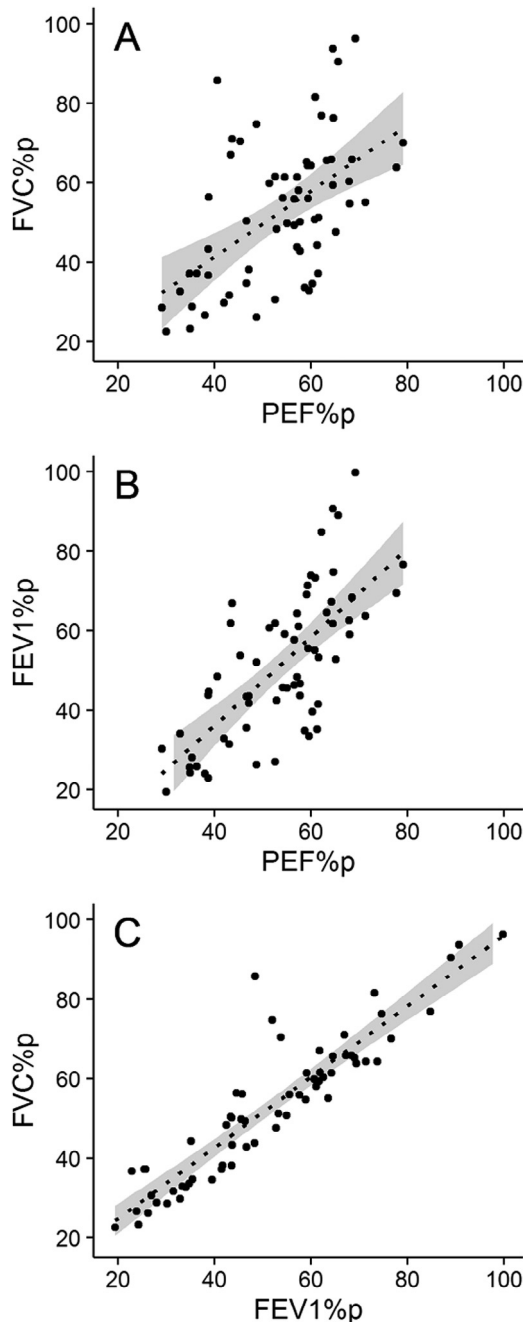| Parameter	ITT population (N = 64)	Subgroup: ≤14 y (N = 32)	Subgroup: >14 y (N = 32)
PEF%p	6.97	6.63	7.29
FVC%p	6.69	8.40	4.36
FEV1%p	11.11	9.75	12.32
MIP%p	18.00	20.74	14.76
MEP%p	15.73	17.76	13.47

Fig. 1. Baseline correlation between dynamic pulmonary function test outcomes. Individual patient data are represented by dots (with regression line); shaded area: 95% confidence interval band.

to assess the influence of age on the ability to perform PFTs. Table 3 also shows that from all available PFTs the lowest CV was measured for PEF%p in the ≤14 year group but for FVC%p in the >14 year group.

In an exploratory analysis the CVs were also calculated for a subpopulation of 58 patients, excluding 6 patients with >10% difference between their highest two FVC values at baseline according to Ref. [18]. The resulting CVs for this subpopulation (N = 58) were comparable to the CVs of the ITT population (N = 64) except for lower CV in FVC%, as expected in this

modified population (Supplementary material Table S2). We also determined the CVs of PFTs for the ITT population with patients separated by baseline Brooke score category (patients in Brooke score categories 1–4: N = 26; Brooke score categories 5,6: N = 38). As shown in Supplementary material Table S3 the CVs for PEF%p and FVC%p were comparable between the two Brooke score subgroups (difference <0.5%), demonstrating again the reliability of these two PFT outcome measures irrespective of the general disease status. In contrast, CVs for FEV1%p, MIP%p and MEP%p differed by more than 3% between these Brooke score subgroups.

3.4. Yearly rate of change in pulmonary function parameters of untreated patients

In order to assess the natural course of disease progression in untreated DMD patients, analyses on the yearly rate of change were conducted for the placebo group of the DELOS trial (N = 33). All flow- (PEF%p) and volume-related (FVC%p; FEV1%p) dynamic pulmonary function parameters showed a statistically significant decline over the course of one year (Table 4). Changes of similar magnitude were observed when patients were split into subgroups of GC-naive patients and those who previously used GC but had stopped at least one year prior to study start. Similarly, the yearly change was comparable in the subgroups split according to the median age at baseline (14 years). Graphical presentations further illustrate the similarity in the change over time in flow- (PEF%p) and volume-related (FVC%p; FEV1%p) PFTs in subgroups split by previous GC use status (Supplementary material Fig. S2) and age category (Supplementary material Fig. S3). These findings demonstrate that age and previous GC use are not discriminating factors for pulmonary disease progression in patients who are in the pulmonary function decline phase (i.e. patients with PEF%p < 80% at the time of enrollment). For MIP%p the yearly rate of decline was slightly smaller in previous GC-users and in the younger age subgroup compared to GC-naive patients and those of older age. MEP%p showed an opposite trend, with larger yearly decline in the previous GC-users and the younger patient subgroup. However, the clinical interpretation of these small differences is unclear. Overall, the yearly decline in maximum static airway pressures was only about half of the magnitude as seen for the dynamic PFT parameters PEF%p, FVC%p and FEV1%p.

3.5. Correlation between pulmonary function and general disease stage

In an attempt to correlate PFTs with general disease progression in this predominantly non-ambulant population, baseline PEF%p, FVC%p and FEV1%p were analyzed separated by a Brooke upper extremity score category (Fig. 2). Although the interpretation of these data is limited by the small number of patients per Brooke score category, a marked drop in all three PFT parameters is apparent at the transition between Brooke score categories 4 and 5. While patients with Brooke scores 1–4 (on average) had PFT results of around 60%–80% of predicted, all average PFTs dropped when patients lost the

Table 4
Yearly rate of change in pulmonary function outcomes (placebo group).

Pulmonary function parameter	All placebo (N = 33)	GC use status (prior GC-use)		Age category (by median)	
		No (N = 14)	Yes (N = 19)	≤14 y (N = 13)	>14 y (N = 20)
PEF%p	−8.9 (2.0)	−10.2 (3.5)	−7.8 (2.7)	−8.6 (3.9)	−8.6 (2.4)
	(−13.0, −4.7)	(−17.7, −2.7)	(−13.5, −2.2)	(−17.2, −0.1)	(−13.7, −3.6)
	$p = 0.0001$	$p = 0.0120$	$p = 0.0090$	$p = 0.0478$	$p = 0.0022$
FVC%p	−8.7 (1.1)	−8.6 (2.1)	−8.7 (1.3)	−10.5 (2.5)	−7.8 (0.8)
	(−11.0, −6.5)	(−13.1, −4.1)	(−11.4, −5.9)	(−16.0, −5.1)	(−9.5, −6.0)
	$p < 0.0001$	$p = 0.0014$	$p < 0.0001$	$p = 0.0014$	$p < 0.0001$
FEV1%p	−10.2 (2.0)	−12.2 (3.6)	−8.7 (1.9)	−9.6 (4.5)	−10.4 (1.6)
	(−14.2, −6.2)	(−20.1, −4.2)	(−12.7, −4.7)	(−19.4, 0.3)	(−13.8, −7.0)
	$p < 0.0001$	$p = 0.0059$	$p = 0.0003$	$p = 0.0554$	$p < 0.0001$
MIP%p	−4.5 (1.3)	−5.8 (2.1)	−3.8 (1.8)	−3.9 (2.3)	−5.1 (1.4)
	(−7.2, −1.8)	(−10.4, −1.3)	(−7.5, −0.0)	(−8.9, 1.1)	(−8.0, −2.1)
	$p = 0.0017$	$p = 0.0164$	$p = 0.0492$	$p = 0.1137$	$p = 0.0023$
MEP%p	−2.8 (1.1)	−2.0 (1.9)	−3.2 (1.5)	−3.4 (2.5)	−2.5 (0.9)
	(−5.1, −0.5)	(−6.1, 2.1)	(−6.4, −0.05)	(−9.0, 2.2)	(−4.5, −0.5)
	$p = 0.0188$	$p = 0.3017$	$p = 0.0466$	$p = 0.2071$	$p = 0.0153$

Data are estimated means from MMRM (SEM) and 95% confidence intervals; *p*-values indicate whether the yearly change was significant.

ability to raise their hand to their mouth (Brooke score 5); this was particularly evident for the volume-related parameters FVC%p and FEV1%p. Available data for Brooke score category 6 were too limited to allow further interpretation of the data.

4. Discussion

This work provides pulmonary function data from a prospectively planned intervention study which enrolled 10–18 year old DMD patients who were in pulmonary function decline stage (defined as PEF%p < 80%) and who did not use glucocorticoids at least 12 months prior to the first assessment (baseline) and during a 12-month follow-up period. Most patients in this study were non-ambulant. Although the interpretation of the data shown here is limited by the sample size (N = 64) and the post-hoc nature of some of the analyses presented, this study with prospective and rigorous data acquisition nevertheless adds to the understanding of the reliability of PFT assessments in adolescent, mostly non-ambulant DMD patients, the natural course of PFT changes and the relation to the general disease status assessed by the Brooke upper extremity function scale.

4.1. Correlation of pulmonary function parameters and reliability of their assessment

Although pulmonary function decline in DMD is typically in a restrictive pattern with low FVC and a normal FEV1/FVC ratio (Tiffeneau index), this work and previous data [15,18] indicate that flow- and volume-related dynamic parameters follow a similar pattern during disease progression and are highly correlated. When expressed as percent of predicted to account for maturational changes PEF%p, FVC%p and FEV1%p are highly correlated and decline approximately linearly with increasing age once patients enter the pulmonary function decline stage. This good correlation between flow- and volume-related parameters has been documented previously [28,29] and is of clinical interest as decline in FVC is an established predictor of morbidity [30]. In the absence of

obstructive lung disease, PEF appears to be an equally valuable measure of disease monitoring and progression of pulmonary function loss in DMD as it assesses maximal expiratory effort as a surrogate measure for expiratory muscle strength.

Our data confirm that in 10–18 year old boys with DMD, PEF%p, FVC%p and FEV1%p can be reliably assessed as seen by the low within-subject CV for assessments taken on an average of 16.7 days (SD 12.4) apart. The two PFT parameters with the best CV (CV: ~7%) were FVC%p and PEF%p, followed by FEV1%p (CV: ~11%). In contrast, CVs for maximum static airway pressures were considerably higher, which may limit the use of MIP%p and MEP%p as pulmonary outcome measures for patients who have reached teenage years. This is in agreement with previous work, which demonstrated that MIP%p and MEP%p did initially decline in patients younger than 15 years and later increased again in patients from the age of 15 years [16]. As shown here, MIP%p and MEP%p consistently have high CVs irrespective of age category or general disease stage and consequently have to be considered less reliable PFTs compared to FVC%p and PEF%p, which has to be considered in clinical interpretation of data obtained from patients in their teenage years.

4.2. Pulmonary function status and evolution is not influenced by previous use of glucocorticoids

There is general agreement that patients with DMD benefit from GC treatment [31,32], which has become the mainstay of neuromuscular management in DMD [33,34]. Specifically, the effect of GC on muscle strength has been shown to prolong ambulation by several years and more recently, continued treatment with GC after the patient becomes non-ambulant has also shown to reduce the risk of progressive scoliosis, stabilize pulmonary function [17,35–37] and delay the loss of upper limb function [38]. An interesting finding of this work was the observation that previous GC use had no long-lasting effect on the decline in pulmonary function. Specifically, patients who had stopped taking GCs at least 12 months and on average 3.7 years prior to the first PFT assessment (i.e. baseline) had
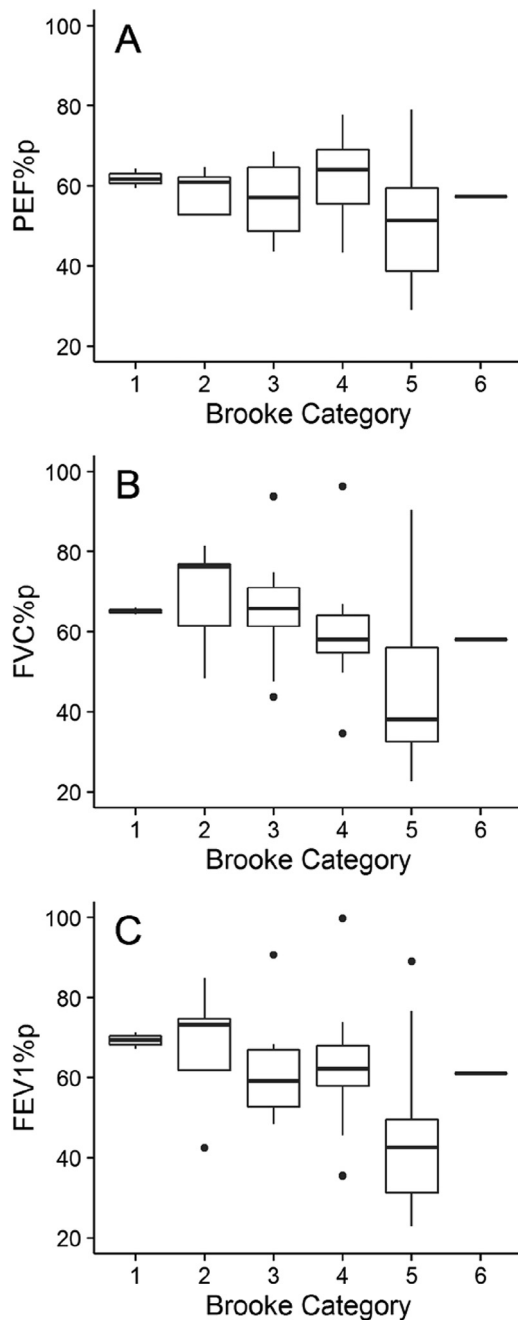
Fig. 2. Pulmonary function by Brooke upper limb function score. Boxplots show medians (quartiles) from descriptive statistics. Brooke category is shown on the X-axis and pulmonary function data as percent predicted on the Y-axis.

PEF%p, FVC%p and FEV1%p comparable to patients who had never used GCs. This is in agreement with previously published data showing that use of GCs can delay the start of pulmonary function decline by 2–3 years [17], but once established, GC use does not alter the rate of decline of pulmonary function, which continues linearly and unabated from the age of approximately 10 years through to the early twenties [17,18]. This is important in light of the well-described risks associated with chronic administration of GCs such as growth retardation, bone demineralization and increased fracture risk, obesity,

hypertension and cataracts, among others [33]. In a natural history study, 42% of DMD patients aged 10 years and older had never used GCs or discontinued their use because of side-effects and tolerability limitations [17], with this proportion increasing in the post-ambulatory phase of the disease.

4.3. Correlation of pulmonary function status with general disease status

Similar to PFT measures, we also found no apparent difference in average Brooke upper extremity function score between past GC-users and GC-naive patients, which is in line with earlier data [17]. An interesting finding of this work was the observation that pulmonary function drops in patients who have reached a Brooke upper extremity function sore of 5, which is in general agreement with earlier data indicating a correlation between upper extremity function loss and decline in FVC [1]. This finding may be of clinical relevance, as it indicates that patients who lose their ability to raise their hand to their mouth may have reached a clinically relevant threshold of lung volume (i.e. FVC%p of 50%), which could be used as an easy-to-assess indicator to identify patients who have reached the stage of advanced pulmonary function loss.

In summary, prospectively collected cross-sectional and longitudinal data from a controlled, multi-center study contribute to the understanding of pulmonary outcome measures in pediatric and adolescent patients with DMD, their correlation and reliability of assessment and their association with general disease status and yearly rate of change. Although the yearly change in FVC%p reported here appears to be most consistent with what is known and accepted in the field, also PEF%p appears to be a reliable marker of flow-related pulmonary function and relevant to provide a comprehensive assessment of the pulmonary function status and decline over time in patients with DMD.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2016.12.014.

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