Interest of SNIP in the longitudinal assessment of young Duchenne muscular dystrophy children

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ASSESSMENTS AND FULL STATISTICAL METHODS

Assessments

Height was measured or estimated from arm span from finger tip to finger tip in patients with kyphoscoliosis [1]. Pressure and volume were measured using the Medisoft Hyp'air compact (Dinant, Belgium). SNIP was measured in an occluded nostril during a maximal sniff through the contralateral nostril. PImax was measured against an obstructed mouthpiece with a small leak to prevent glottic closure, at functional residual capacity (FRC), maintaining maximal pressure for at least 1 second. Slow VC was measured according to standard procedures [2, 3]. At least ten (most often, 15 to 20) maximal sniffs, both performed from FRC [4] and at least five PImax measurements were obtained. The highest SNIP (from a sniff less than 500 ms in duration) and PImax were used. Arterialized capillary oxygen (PaO_2) and carbon dioxide pressures ($PaCO_2$) were measured at the ear lobe (ABL 715, Radiometer, Copenhagen, Denmark). These results were included in the online supplement since significant deteriorations in lung volumes and inspiratory pressures were observed in the older DMD patients. Predicted values were those of Cook and Haman [5] for lung volume (VC) as recommended for use in children and adolescents [6], those of Gaultier et al. for arterialized capillary carbon dioxide and capillary oxygen pressures [7] and those of Stefanutti and Fitting [8] for SNIP and PImax. Baseline results were expressed as z-scores or as standardized residuals, i.e. ((recorded-predicted)/residual standard deviation from regression line of reference values).

Statistics

Median and quartiles (or range) are presented for continuous variables and percentages for categorical variables. At inclusion, within-session repeatability was evaluated by intraclass correlation coefficient (ICC) and, for sniff nasal inspiratory pressure (SNIP) and maximal

inspiratory pressure (PImax), by the coefficient of variation (CoV); for slow vital capacity (VC), the difference between the largest and the next largest manoeuvre was used to this effect. Median values were compared by a paired on unpaired Wilcoxon test, the correlation between SNIP/PImax ratio and VC was assessed using a Spearman correlation test.

According to the trend (LOESS SAS procedure), we chose a linear or quadratic age effect. Analysis of longitudinal data was performed using Linear Mixed Model (LMM)[9]. The model included a fixed effect for the dystrophinopathy phenotype (Becker, BMD or Duchenne muscular dystrophy, DMD), age, age², age dystrophinopathy phenotype and age²* dystrophinopathy phenotype for quadratic model and a random effect for intercept and age. A spatial power covariance was used in each model as this structure yielded the lowest values of Akaike's Information Criterion (AIC). The ESTIMATE statement was used to compare mean predicted values between both dystrophinopathy phenotypes for specific age.*

Scoliosis is a frequent complication in DMD. Thoracic scoliosis reduces respiratory muscle efficiency by impeding movement of the ribs, placing the respiratory muscles at a mechanical disadvantage. As, in our study, scoliosis score was significantly correlated to age (co-linearity), scoliosis magnitude was not introduced in the analysis of the evolution of pressures and volume with age.

Statistical analysis was performed by means of SAS software (SAS system, version 9.2, SAS Institute Inc., Cary, NC 25513).

FULL VOLUME, PRESSURE, ARTERIALIZED CAPILLARY CARBON DIOXIDE AND CAPILLARY OXYGEN PRESSURES RESULTS

Data at inclusion

As compared with the BMD group, arterialized capillary carbon dioxide ($PaCO_2$) and capillary oxygen pressures (PaO_2) values were comparable in the Duchenne muscular dystrophy group (Table E1) (although three DMD individuals had low PaO_2 values (<2 z-scores)).

Longitudinal data

Actual follow-up duration at each scheduled visit is shown in Table E2.

The dystrophinopathy phenotype (BMD versus DMD) did not influence de the SNIP/PImax ratio evolution with age (p=0.904). SNIP/PImax ratio was >1 in all children less than 10 years of age. A linear decrease was significant for the SNIP/PImax ratio evolution with age (Figure 1 in text).

In contrast, a significant effect of the type of dystrophinopathy phenotype on SNIP (p=0.002), PImax (p<0.001), VC (p<0.001) and PaO_2 (p=0.013) age-related changes was observed (i.e. interaction age*dystrophinopathy phenotype or age^2*dystrophinopathy phenotype was significant). These results are therefore described separately for BMD and DMD.

BMD data. SNIP, PImax and VC increased with age (Figures 2, 3 and 4 in text). A curvilinear linear effect was significant for the SNIP and the VC evolutions with age. A linear effect was significant for the PImax evolution with age. Reduced inspiratory pressures during the follow-up (Figures 2 and 3 in text) were noted for patient 29, 16 years at inclusion, with cramps and

myalgia while walking small distance (100 m) and falls as chief complaints, though this patient remained ambulatory at the end of the follow-up.

PaO_2 did not decrease (p=0.207) and $PaCO_2$ did not increase with age (p=0.071) among BMD children.

DMD data. The analysis of the individual age-related change in measurements showed an increase in SNIP and VC followed by a decline in these values. This curvilinearity was confirmed by statistics (significant quadratic effect for SNIP, p=0.039, Figure 2 in text, and for VC, p=0.0043, Figure 4 in text). Lower SNIP values were observed in the DMD group compared with the BMD group from the age of 6.2 years (p<0.050, vertical line in Figure 2 in text) and lower VC from the age of 9.1 years was evident in DMD versus BMD (p <0.050, vertical line in Figure 4 in text).

While an increase in PImax with age was observed in BMD, LMM analysis showed no change in PImax with age (p=0.665) in DMD. Therefore, compared with the BMD group, lower PImax values were observed in the DMD group from 9.5 years of age, p <0.050, Figure 3 in text.

Within the DMD group, age at NIV initiation was tested as dummy variable: =0 if age at NIV initiation <17 years, =1 if age ≥ 17 years. A less favourable evolution in SNIP and VC values was observed when NIV was initiated before 17 years (Figure 5 in text): DMD children with NIV initiated before the age of 17 years exhibited a lower SNIP and a lower VC from the age of, respectively, 11.5 and 13.0 years. In contrast, age-related changes in PImax were not related to the need of NIV prior to 17 years of age.

Diurnal PaO_2 decreased with age (PaO_2, mmHg = 95.5 - 0.516 Age (years), p=0.025) in DMD but not in BMD. Thus, compared with the BMD group, lower PaO_2 values were observed in the DMD group from the age of 11.9 years, p =0.0477.

Diurnal $PaCO_2$ increased with age ($PaCO_2$, mmHg = 33.9 + 0.388 Age (years), $p<0.001$) in the DMD group, however most values remained in the normal range and $PaCO_2$ values in DMD were not significantly higher than values in BMD. At the end of the follow-up, hypercapnia (≥ 45 mmHg) was present in three subjects, 17 to 20 year-old, with VC <1.400 L, PImax <40 cmH_2O and SNIP <60 cmH_2O.

DISCUSSION

The utility of linear mixed modelling

This is the first prospective study using a statistical analysis (LMM) taking into account the longitudinal aspects of the data to study the individual pattern of age-related changes of pulmonary function in BMD and DMD patients. It has the benefit of providing an accurate assessment of the age-related change of pressure and volume in each dystrophinopathy phenotype. Indeed, assessment of change in pulmonary function over time was derived from measurements of change for individuals (between-individual variability in pulmonary function levels did not contribute to the variability of individual rate of change). In addition, individuals served as their own controls. This effectively increased statistical power and precision [10]. LMM analysis also allowed the comparison of pressure and volume change between dystrophinopathy phenotypes.

Arterialized capillary carbon dioxide and capillary oxygen pressures

Diurnal hypercapnia was observed in very few (10%) of our DMD children, 15.1, to 19.9-year-old. In the absence of primary respiratory disease, diurnal chronic hypercapnia characterizes the late stages of neuromuscular diseases [11, 12]. Hypercapnia was observed in patients with proximal myopathies when VC was <50% and respiratory muscle strength

<40% predicted [13]. It was observed in few (4%) DMD children, 15 to 21-years old, with forced VC ranging between 9% and 47% predicted [12]. Selective preservation of inspiratory muscle strength compared to expiratory muscle strength, and related to late involvement of the diaphragm, may account for the ability of DMD patients to maintain normal $PaCO_2$ until a very late stage of the disease [14].

Conversely, PaO_2 decreased slightly with age and became significantly lower compared with the BMD group from 11.5 years of age. Low PaO_2 without concomitant hypercapnia, together with a decrease in lung compliance, was explained by the presence of atelectasis in a group of DMD on non-invasive ventilation [15].

Table E1 Baseline data of the 43 children included in the study

		BMD (n=10)		DMD (n=33)		Wilcoxon
		Median	*(min ; max)*	*median*	*(min ; max)*	*P*
Raw data	PaO_2 (mmHg)	93	(85 ; 103)	92	(80 ; 98)	0.4297
	$PaCO_2$ (mmHg)	38	(36 ; 40)	38	(31 ; 43)	0.7903
Z-scores	PaO_2	0.01	(-2.10 ; 2.02)	-0.08	(-3.00 ; 2.06)	0.6378
	$PaCO_2$	0.14	(-0.20 ; 0.75)	0.19	(-1.45 ; 1.58)	0.7903

Values are expressed as raw values or as z-scores or standardised residual i.e. ((recorded-predicted)/residual standard deviation from regression line of reference values [7]). BMD/DMD: Becker/Duchenne muscular dystrophy. $PaCO_2$: arterialized capillary oxygen and carbon dioxide pressures.

Table E2 Mean follow-up duration for each scheduled visit

N	Scheduled time (year)	Actual time (year)		
		Median	Q_1	Q_3
43	0.0	0.0	0.0	0.0
40	0.5	0.5	0.5	0.5
32	1.5	1.5	1.5	1.6
40	2.0	2.0	2.0	2.1
34	2.5	2.5	2.5	2.6
41	3.0	3.1	3.0	3.2

Q_1-Q_3: first and third quartile. N: number of children assessed at each scheduled time.

REFERENCES

1. Linderholm H, Lindgren U. Prediction of spirometric values in patients with scoliosis. *Acta orthopaedica Scandinavica*. 1978;49:469-74.

2. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J*. 2005;26:319-38.

3. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl*. 1993;16:5-40.

4. Lofaso F, Nicot F, Lejaille M, Falaize L, Louis A, Clement A, Raphael JC, Orlikowski D, Fauroux B. Sniff nasal inspiratory pressure: what is the optimal number of sniffs? *Eur Respir J*. 2006;27:980-2.

5. Cook CD, Hamann JF. Relation of lung volumes to height in healthy persons between the ages of 5 and 38 years. *J Pediatr*. 1961;59:710-4.

6. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. *Eur Respir J*. 1995;8:492-506.

7. Gaultier C, Boule M, Allaire Y, Clement A, Buvry A, Girard F. Determination of capillary oxygen tension in infants and children: assessment of methodology and normal values during growth. *Bull Eur Physiopathol Respir*. 1979;14:287-97.

8. Stefanutti D, Fitting JW. Sniff nasal inspiratory pressure. Reference values in Caucasian children. *Am J Respir Crit Care Med*. 1999;159:107-11.

9. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. *Stat Med*. 1997;16:2349-80.

10. Weiss ST, Ware JH. Overview of issues in the longitudinal analysis of respiratory data. *Am J Respir Crit Care Med*. 1996;154:S208-11.

11. Baydur A. Respiratory muscle strength and control of ventilation in patients with neuromuscular disease. *Chest*. 1991;99:330-8.

12. Canny GJ, Szeinberg A, Koreska J, Levison H. Hypercapnia in relation to pulmonary function in Duchenne muscular dystrophy. *Pediatr Pulmonol*. 1989;6:169-71.

13. Braun NM, Arora NS, Rochester DF. Respiratory muscle and pulmonary function in polymyositis and other proximal myopathies. *Thorax*. 1983;38:616-23.

14. Inkley SR, Oldenburg FC, Vignos PJ, Jr. Pulmonary function in Duchenne muscular dystrophy related to stage of disease. *Am J Med*. 1974;56:297-306.

15. Nicot F, Hart N, Forin V, Boule M, Clement A, Polkey MI, Lofaso F, Fauroux B. Respiratory muscle testing: a valuable tool for children with neuromuscular disorders. *Am J Respir Crit Care Med*. 2006;174:67-74.