Sniff nasal inspiratory pressure in the longitudinal assessment of young Duchenne muscular dystrophy children

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ABSTRACT Traditional measures of respiratory function in children with Duchenne muscular dystrophy (DMD) are based on maximal inspiratory pressure (P_{Imax}) and vital capacity (VC). Sniff nasal inspiratory pressure (SNIP) measurements are easily performed by young children with neuromuscular disorders. The clinical value of SNIP in the longitudinal assessment of respiratory weakness remains to be assessed. The objective of the present study was to assess longitudinally the changes in SNIP, P_{Imax} and VC with age in DMD children. We hypothesised that their longitudinal assessment would show an earlier decline in SNIP than VC.

A 3-year, prospective follow-up, at 6-month intervals of, 33 steroid-naïve, 5–20-year-old DMD patients was analysed using a linear mixed model.

SNIP measurements were reliable (within-session coefficient of variation 8%). SNIP and VC increased until 10.5 and 12.5 years of age, respectively, and declined thereafter, while P_{Imax} did not change with age.

SNIP was an earlier marker of decline in respiratory muscle strength (at 10.5 years) than VC (at 12.5 years) in young DMD patients. SNIP longitudinal assessment is useful in the detection of inspiratory strength decline in young DMD patients when VC values remain within normal values and as an outcome measure in clinical trials for emerging therapeutics in young DMD patients from the age of 5 years.

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Introduction

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD), the most common neuromuscular diseases in children, occur as a result of mutations in the dystrophin gene, with BMD having a milder phenotypic expression [1]. Respiratory impairment in neuromuscular diseases is assessed by the measurement of maximal inspiratory pressure (P_{Imax}), slow vital capacity (VC) and, more recently, sniff nasal inspiratory pressure (SNIP). Studies describing longitudinal follow-up of respiratory function for $\geqslant$2 years in children with BMD or DMD have been based on P_{Imax} measurements [2–4] and lung volumes [2–7]. At the time of writing, there was no published prospective study describing longitudinal assessment of inspiratory muscle strength by SNIP measurements. SNIP has the advantage of measuring inspiratory pressure during a natural manoeuvre that is easily performed even by young children with neuromuscular disorders [8, 9] and may prove to be more reliable in BMD/DMD children than P_{Imax}. Moreover, based on the shape of the normal pressure–volume curve, a loss of respiratory muscle strength is expected before a fall in VC and other lung volumes [10]. Therefore, SNIP measurement may detect the respiratory muscle strength decrease earlier in the disease or in younger children than P_{Imax} or VC, and could prove to be a more sensitive outcome measurement specifically evaluating inspiratory muscle strength. Therefore, the aim of the study was to assess inspiratory pressure and volume change with age in BMD and non-steroid treated DMD children in order to: 1) document the natural evolution of SNIP measurement in these phenotypes, and 2) identify the ages of decline in SNIP, P_{Imax} and VC in DMD children by using a statistical analysis adapted to longitudinal data. Our hypothesis was that the longitudinal assessment of these parameters would show an earlier decline in SNIP than VC in DMD children.

Subjects and methods

Subjects

Twice-yearly evaluation of lung volume and inspiratory muscle strength over a period of 3 years was proposed to 51 BMD/DMD children by their neuropaediatrician between June 2002 and April 2006. Included children had BMD/DMD confirmed by muscle biopsy (dystrophin of altered size and/or abundance for BMD, and absence of dystrophin for DMD), an age $\geqslant$3 years and all were able to perform sniff manoeuvres adequate for SNIP measurement. One BMD patient refused to participate. Four BMD and three DMD patients unable to perform acceptable sniff manoeuvres were excluded. 43 children, 10 BMD (all ambulatory at inclusion) and 33 DMD (none treated with steroids, 13 ambulatory at inclusion), were included. Confirmation of diagnosis by genetic testing for a dystrophin gene mutation was obtained in nine BMD and 32 DMD cases.

Pulmonary function tests (PFTs) and arterialised capillary blood gas analyses (online supplementary material), none performed within 8 weeks following a respiratory tract infection, were obtained from June 2002 to May 2009. The study was approved by the ethical committee of our institution (Comité Consultatif de Protection des Personnes se Prêtant à la Recherche Biomédicale du CHRU de Lille, Lille, France) on March 6, 2001. All parents and patients signed a consent form for participation in the study.

Assessments

Height was measured, or estimated from arm span (from fingertip to fingertip) in patients with kyphoscoliosis [11].

SNIP was measured in an occluded nostril during a maximal sniff through the contralateral nostril; P_{Imax} was measured against an obstructed mouthpiece with a small leak to prevent glottic closure, at functional residual capacity (FRC), maintaining maximal pressure for $\geqslant$1 s, and slow VC was measured according to standard procedures [12] using Hyp Air Compact (Medisoft, Dinant, Belgium). At least 10 (most often, 15–20) maximal sniffs, performed from FRC [13], and at least five P_{Imax} measurements were obtained. The highest SNIP (from a sniff $<$500 ms in duration) and P_{Imax} were used. Baseline results were expressed as z-scores (online supplementary material).

Statistics

Median (interquartile range or range) are presented for continuous variables and percentages for categorical variables. At inclusion, for P_{Imax} and SNIP, the within-session repeatability was evaluated by two indices: coefficient of variation (CoV), the index of repeatability that is most frequently used in PFTs; and intraclass correlation coefficient (ICC), which has the advantage over CoV of being adjusted for the effects of the scale of measurements and, for VC, by the difference between the largest and the next-largest manoeuvre. Median values were compared by a paired or unpaired Wilcoxon test, the correlation between SNIP/P_{Imax} ratio and VC was assessed using a Spearman's correlation test. Analysis of longitudinal data was performed using a linear mixed model (LMM) [14].

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TABLE 1 Baseline data of the 43 children included in the study

	BMD[#]	DMD[¶]	Wilcoxon p-value
Age years	12.5 (5.4–16.4)	11.0 (5.0–16.7)	0.1500
Height cm	149 (116–181)	136 (103–170)	0.0430
Weight kg	43.8 (22.0–93.0)	29.5 (17.0–80)	0.0540
BMI kg·m^{-2}	20.1 (15.2–33.7)	16.5 (12.5–33.8)	0.0540
BMI z-score[+]	0.2 (-0.7–4.8)	-0.1 (-4.8–6.3)	0.2200
Raw data			
SNIP cmH_2O	72 (45–148)	48 (22–80)	0.0003
*P*Imax cmH_2O	76 (44–146)	38 (17–75)	0.0008
Slow VC L	2.62 (1.45–5.36)	1.70 (0.77–2.11)	<0.0001
SNIP/*P*Imax	1.08 (0.59–1.71)	1.17 (0.65–2.35)	0.2440
Z-scores			
SNIP	-1.40 (-3.26–1.05)	-2.20 (-4.24– -0.91)	0.0055
*P*Imax	-0.91 (-3.91–1.57)	-2.63 (-5.27– -0.28)	0.0178
VC	-1.19 (-1.81–0.00)	-2.20 (-6.25–1.23)	0.0259

Data are presented as median (range), unless otherwise stated. Values are expressed as raw values, or as z-scores *i.e.* ([recorded-predicted]/residual standard deviation from regression line of reference values). BMD: Becker muscular dystrophy; DMD: Duchenne muscular dystrophy; BMI: body mass index; SNIP: sniff nasal inspiratory pressure; *P*Imax: maximal inspiratory pressure; VC: vital capacity. [#]: n=10; [¶]: n=33; [+]: calculated according to [15].

Results

BMD characteristics

Anthropometric data of our population are detailed in table 1. Genetic testing, obtained in nine of the 10 BMD patients, showed that six of them had a deletion within central rod domain II: five patients had deletions around exons 45–53, generally associated with typical BMD [16], and were all ambulatory at last visit (median age 14 years, range 12–17 years), while one patient had a deletion in the proximal portion of this domain (exons 13–41) (patient 29: 16 years at inclusion, with cramps and myalgia while walking small distances and falls as chief complaints, though remaining ambulatory at the end of the follow-up). In three BMD children from the same family (patients 34–36), a deletion in domain I (exons 3–7 of the dystrophin gene) was detected, which has been previously associated with a more severe phenotype [16]; progression was more severe for patient 34, with loss of ambulation at 16 years of age.

DMD characteristics

Ambulation was lost at a median age of 9.4 years (interquartile range 8.3–10.4 years). Scoliosis developed in 61% of DMD patients during the follow-up: Cobb angle remained <30° in 30% of patients, ranged from 30° to 50° in 30% and was >50° in 1%. Spine fusion was performed in 36% of the nonambulatory patients with spinal curvature >30° [17, 18] at a median age of 13.2 years (interquartile range 12.5–13.8 years). Nocturnal noninvasive ventilation (NIV) had been initiated in one subject before the beginning of the study. Follow-up until June 2012 showed that NIV was initiated in 10 subjects before the age of 17 years (the mean age for the development of overnight hypercapnia requiring night NIV in a larger DMD population [19]) and in 13 patients after 17 years of age.

Data at inclusion

SNIP and VC measurements were obtained in 100% of the children and *P*Imax in 88% (inclusion criteria). In the BMD group, SNIP, *P*Imax and VC were abnormal (<2 z-scores) in two, four and none of the patients, respectively. In the DMD group, SNIP, *P*Imax and VC were abnormal in 21, 23 and 17 patients, respectively. Pressure and volume measurements were lower in the DMD group compared with the BMD group (table 1), while ages were comparable. SNIP/*P*Imax ratios values were comparable in both the BMD and DMD groups, with values ⩾1 in 68% of patients, but were not correlated with VC z-scores (Spearman r=0.087, p=0.605). Repeatability of baseline measurements is reported in table 2: the within-session reproducibility was significantly better for SNIP than for *P*Imax.

Longitudinal data

The phenotype (BMD *versus* DMD) did not influence the evolution of SNIP/*P*Imax with age (p=0.904). A linear decrease was significant for SNIP/*P*Imax evolution with age and SNIP/*P*Imax was >1 in all children up to 10 years of age (fig. 1).

TABLE 2 Repeatability of baseline measurements of the 43 children included in the study

	Children in whom the parameter was measured n (%)	Repeatability		ICC (95% CI)
		Criterion	Median (interquartile range)	
SNIP	43 (100)	CoV %	8# (6–11)	0.96 (0.92–0.98)
***P*Imax**	38 (88)	CoV %	10# (6–20)	0.90 (0.83–0.95)
Slow VC	43 (100)	Δ mL	75 (40–151)	0.99 (0.98–0.99)
		Δ %	5 (2–9)	

ICC: interclass correlation coefficient; SNIP: sniff nasal inspiratory pressure; *P*Imax: maximal inspiratory pressure; VC: vital capacity; CoV: coefficient of variation; Δ: difference between the two best measurements obtained in each child (expressed in millilitres or percentage of the best value). #: within-session reproducibility evaluated by the CoV was significantly better for SNIP than for *P*Imax (p=0.013).

In contrast, a significant effect of phenotype on age-related changes in SNIP (p=0.002), *P*Imax (p<0.001) and VC (p<0.001) was observed. These results are therefore described separately for BMD and DMD.

BMD data

SNIP, *P*Imax and VC increased with age (figs 2–4). Reduced inspiratory pressures during follow-up (figs 2 and 3) were noted only for patient 29.

DMD data

SNIP and VC increased until 10.5 and 12.5 years, respectively, and then decreased (figs 2 and 4). Lower SNIP and VC values were observed compared with the BMD group from the age of 6.2 and 9.1 years, respectively.

While a *P*Imax increase with age was observed in BMD patients, LMM analysis showed no change in *P*Imax with age in DMD; compared with the BMD group, lower *P*Imax values were thus observed in the DMD group from the age of 9.5 years (fig. 3).

DMD children with NIV initiated before the age of 17 years exhibited a lower SNIP and a lower VC from the age of 11.5 and 13.0 years, respectively (fig. 5). In contrast, age-related changes in *P*Imax were not related to the need for NIV prior to 17 years of age.

Discussion

This study is first to document the natural evolution of SNIP in non-steroid treated DMD and in BMD children. It shows that SNIP measurements are repeatable (table 2) and that the individual age-related SNIP

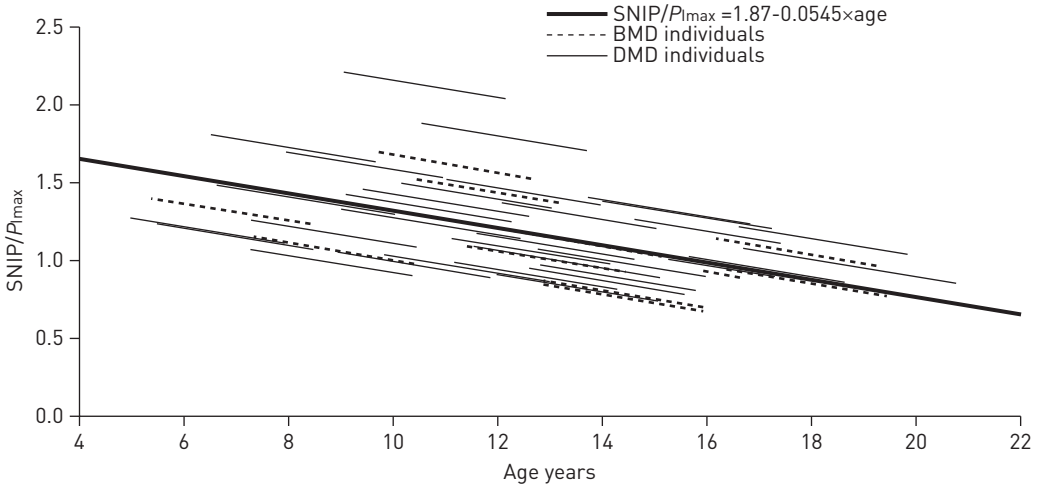

FIGURE 1 Plot of the regression line for the whole population (thick line) and individual regression lines resulting from the mixed model analysis using the sniff nasal inspiratory pressure (SNIP)/maximal inspiratory pressure (*P*Imax) ratio values for the 10 Becker muscular dystrophy (BMD) and the 33 Duchenne muscular dystrophy (DMD) individuals. Longitudinal assessment showed that SNIP/*P*Imax decreased with age. A linear effect was significant for the evolution of SNIP/*P*Imax with age (p<0.001). The dystrophinopathy phenotype (BMD *versus* DMD) did not influence the evolution of SNIP/*P*Imax with age (p=0.904). SNIP/*P*Imax was >1 in all children up to 10 years of age.

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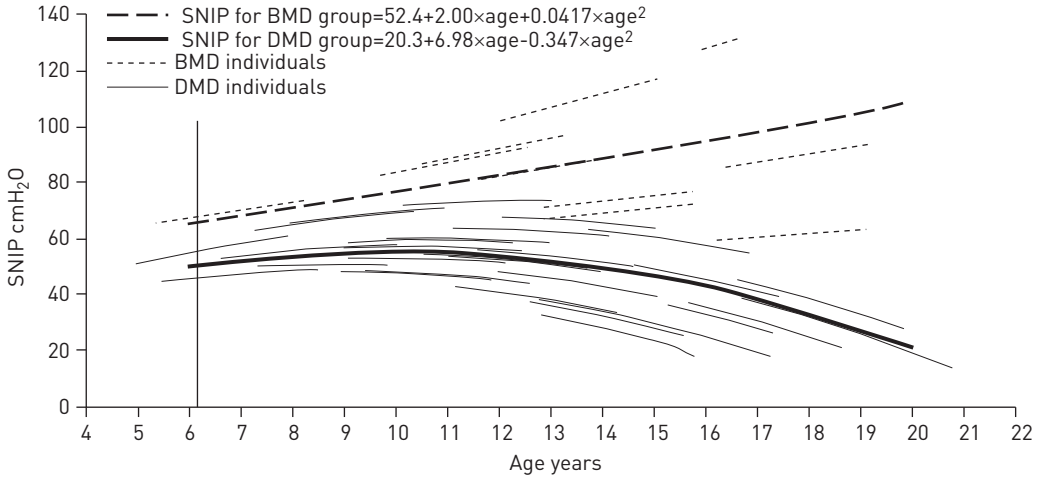

FIGURE 2 Plot of the regression line (thick lines) for each dystrophinopathy phenotype and individual regression lines (thin lines) resulting from the mixed model analysis using the 257 sniff nasal inspiratory pressure (SNIP) values for the 10 Becker muscular dystrophy (BMD) and the 33 Duchenne muscular dystrophy (DMD) individuals. A significant effect of the dystrophinopathy phenotype on age-related SNIP changes was observed ($p=0.002$). Longitudinal assessment in children with BMD showed that SNIP increased with age. A curvilinear effect was significant for SNIP evolution with age. In DMD patients, the graphic analysis of the longitudinal individual profiles of SNIP showed an increase until 10.5 years, reaching a pressure of 55 cmH_2O, followed by a decline with age. This curvilinearity was statistically confirmed ($p=0.039$). According to the mathematical model, compared with the BMD group, significantly lower SNIP values were observed in the DMD group from the age of 6.2 years (vertical line, $p<0.050$).

changes reflect the severity of the DMD subphenotype. It provides more accurate assessment (online supplementary material) of age-related P_{Imax} and VC changes in both phenotypes of this dystrophinopathy and in younger children (5-year-olds) than previous studies. It emphasises the differences in age-related pressure and volume changes between BMD and DMD phenotypes. Using a statistical method that is adapted to our longitudinal study design, we identified the ages of inspiratory pressure and volume decline in DMD children. We show the following. 1) In BMD, SNIP, P_{Imax} and VC increase up to 20 years of age. In DMD, SNIP and VC increase until 10.5 and 12.5 years, and decline thereafter, and no age-related P_{Imax} change is observed. 2) The age-related pressure and volume changes therefore differ between BMD and DMD. Compared with BMD, lower pressure and volume is observed in DMD from the age of 6.2 to

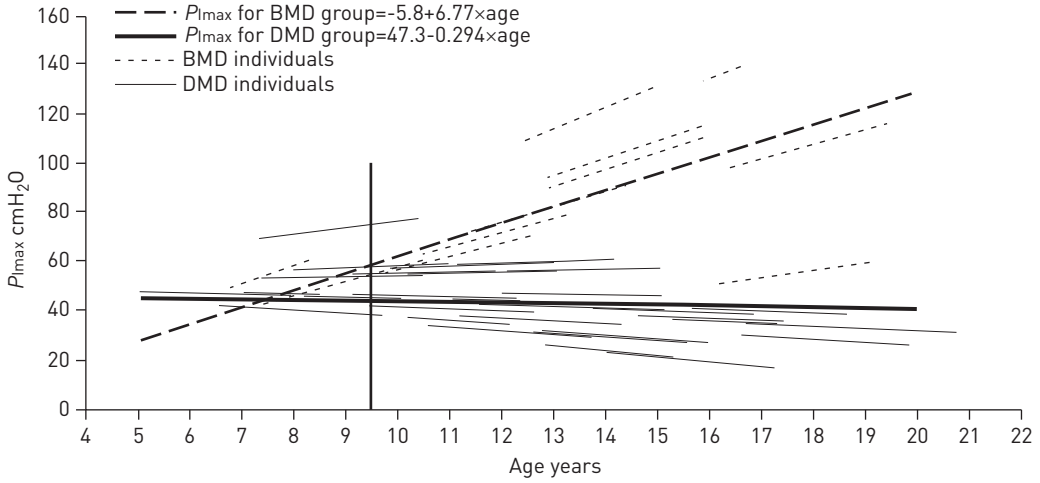

FIGURE 3 Plot of the regression line (thick lines) for each dystrophinopathy phenotype and individual regression lines resulting from the mixed model analysis using the 257 maximal inspiratory pressure (P_{Imax}) values for the 10 Becker muscular dystrophy (BMD) and the 33 Duchenne muscular dystrophy (DMD) individuals. A significant effect of the dystrophinopathy phenotype on age-related P_{Imax} changes was observed ($p<0.001$). Longitudinal assessment in children with BMD showed that P_{Imax} increased with age. A linear effect was significant for the evolution of P_{Imax} with age. In children with DMD, the graphical analysis of the longitudinal individual profiles of P_{Imax} showed no relationship with age from 5 to 20 years ($p=0.665$). According to the mathematical model generated, compared with the BMD group, significantly lower P_{Imax} values were observed in the DMD group from 9.5 years of age (vertical line, $p<0.050$).

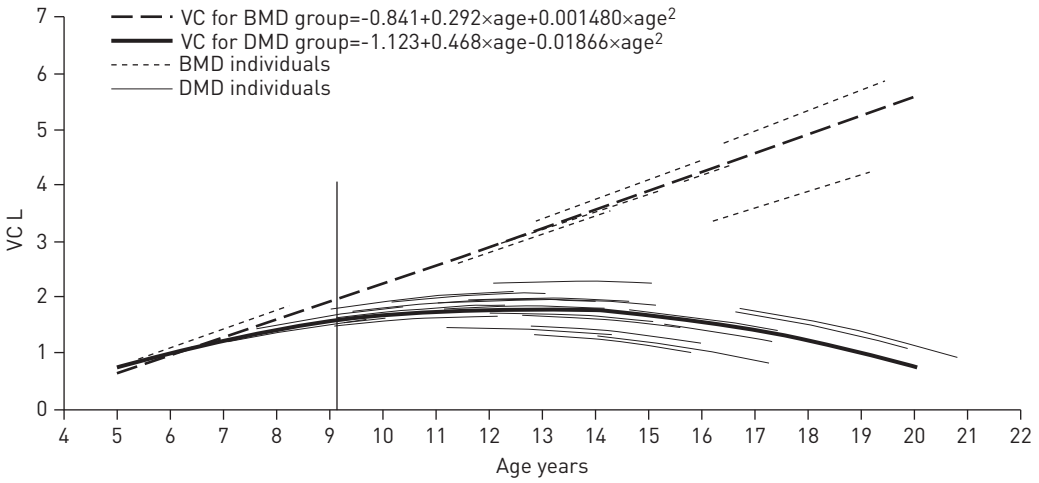

FIGURE 4 Plot of the regression line (thick lines) for each dystrophinopathy phenotype and individual regression lines resulting from the mixed model analysis using the 270 slow vital capacity (VC) values for the 10 Becker muscular dystrophy (BMD) and 33 Duchenne muscular dystrophy (DMD) individuals. A significant effect of the dystrophinopathy phenotype on VC ($p<0.001$) was observed. Longitudinal assessment of VC in children with BMD showed that VC values increased from 5 to 20 years of age. In children with DMD, an increase in VC was observed until 12.5 years, reaching a volume of 1.82 L, followed by a decrease in these measurements. According to the mathematical model, compared with the BMD group, significant lower VC values were observed in the DMD group from the age of 9.1 years (vertical line, $p<0.05$).

9.5 years, with lower SNIP values being observed from an earlier age (6.2 years) than *P*Imax (9.5 years) or VC (9.1 years). The SNIP decline was therefore an earlier sign of the decline of inspiratory muscle strength in DMD than the decline of slow VC or *P*Imax.

Baseline data

Our data support the use of SNIP to assess inspiratory muscle strength in young children with neuromuscular disease. Many children with neuromuscular disease find it easier to perform a sniffing [8, 9] than a static manoeuvre [9] and our study found that BDM/DMD children exhibit a higher within-session reproducibility in performing SNIP (CoV 8%) than *P*Imax manoeuvres. The SNIP and *P*Imax ICC values (higher for SNIP than *P*Imax measurements) were consistent with those of CoV. The cognitive impairment that may be present in DMD may explain the higher variability in performing *P*Imax manoeuvres [20], while the excellent SNIP repeatability in our study may be ascribed to the fact that sniff manoeuvres were performed with a visual feedback and that $\geqslant$10 manoeuvres were performed. Indeed, a plateau in pressure is reached after five to 10 sniffs in most individuals and a more repeatable measure of maximum SNIP is obtained with >10 sniffs [13]. We therefore adopted this approach in our study, in line with the recommendations of LOFASO *et al.* [13] for the longitudinal monitoring of inspiratory muscle strength. As a result, the SNIP repeatability in our BMD/DMD children was better than that observed in healthy children (16–17%, 10 sniffs without visual feedback) [21] or in 5–50-year-old subjects with neuromuscular disorders (20%, 10 sniffs without visual feedback) [9] but close to that reported in healthy adults (6% and 10% with 10 and 12 sniffs, respectively, without visual feed-back) [22, 23].

Moreover, at inclusion, SNIP seemed to accurately reflect inspiratory muscle strength, as it was equal to or greater than *P*Imax in 68% of our BMD/DMD patients, a proportion similar to that observed in children with neuromuscular disorders [9] but higher than that observed in an adult neuromuscular population (49%) [24]. SNIP/*P*Imax at inclusion was not related to VC and our results for BMD/DMD children are therefore inconsistent with those of HART *et al.* [24] but only two (6%) of our DMD children had VC <40% predicted as compared with 37% of their adult subjects.

BMD longitudinal data

SNIP and PImax

Our study has the originality of documenting the natural evolution of SNIP in BMD patients. It was interesting to obtain the same PFT assessments, including SNIP and *P*Imax measurements, with the same schedule, in children with BMD and in children with the same dystrophinopathy but a more severe clinical phenotypic expression (DMD). In BMD, it showed that SNIP, like *P*Imax, increases until 20 years of age. However, in one patient with a more severe clinical BMD subphenotype, we observed an early decline in SNIP and *P*Imax suggesting that these parameters should be evaluated in such patients.

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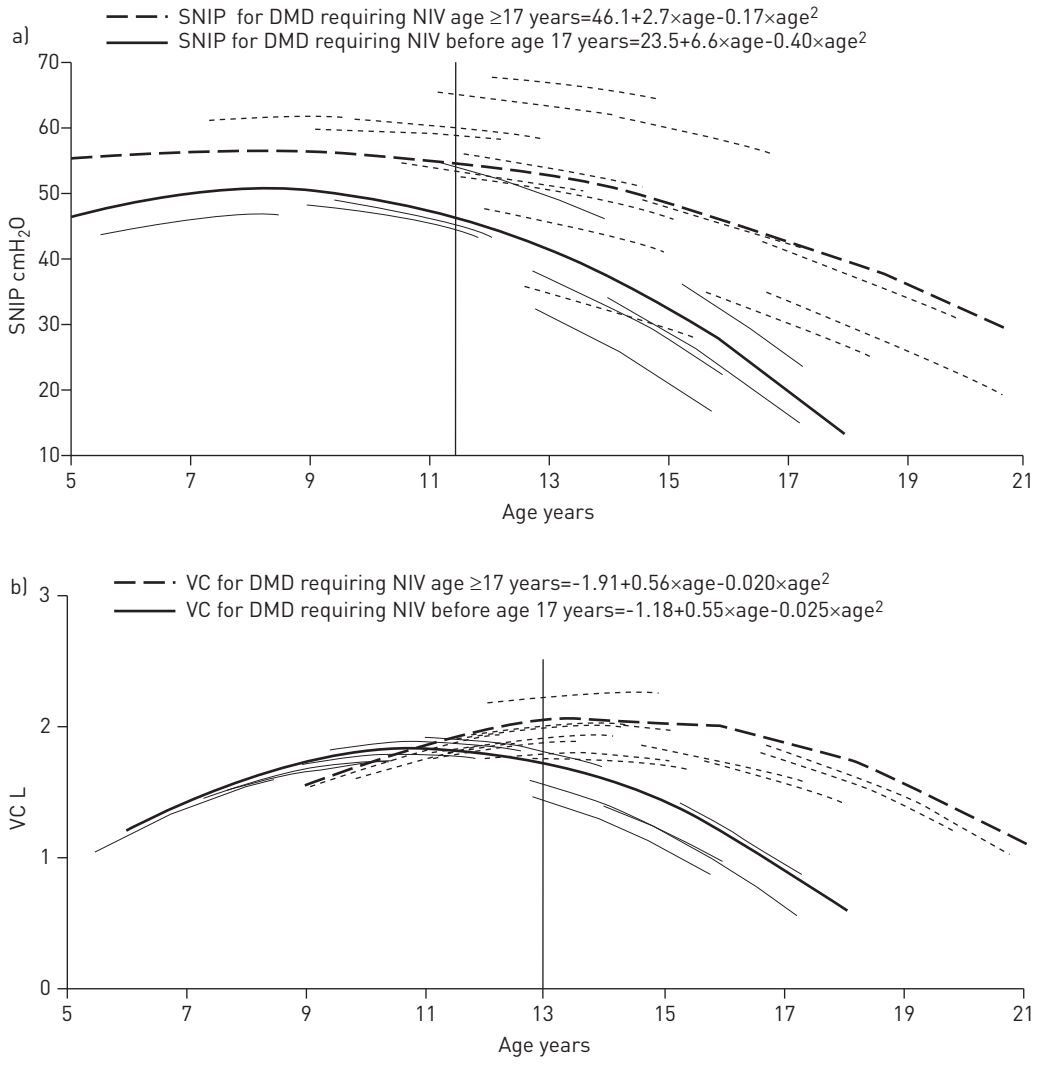

FIGURE 5 Plot of the regression lines (thick lines) for 23 Duchenne muscular dystrophy (DMD) patients according to the initiation of noninvasive ventilation (NIV) before or after the age of 17 years and individual regression lines resulting from the mixed model analysis using a) sniff nasal inspiratory pressure (SNIP) values and b) vital capacity (VC) values. DMD children with NIV before the age of 17 years exhibited a lower SNIP from the age of 11.5 years (vertical line) and a lower VC from the age of 13 years (both $p<0.05$).

Vital capacity

VC does not seem to be able to detect more severe clinical BMD subphenotypes, as an increase in slow VC was observed until 20 years of age in all our BMD patients (including patient 29), in agreement with the data of McDonald *et al.* [3].

DMD longitudinal data

Sniff inspiratory pressure

The sniff manoeuvre has proved to be valuable in assessing diaphragm strength using transdiaphragmatic pressure (P_{di}) [25] and weakness of the diaphragm was detected by measurement of sniff P_{di} in ~13-year-old DMD subjects (cross-sectional evaluation). SNIP was thus proposed as a noninvasive test of inspiratory muscle strength [26]. Our longitudinal study is the first to document the natural evolution of SNIP in steroid-naïve DMD children. In addition, it showed that, in DMD, the decline of inspiratory muscle strength evaluated with SNIP occurred earlier (at 10.5 years) than the VC decline (12.5 years). Moreover, comparing the age-related pressure and volume changes in DMD to those observed in the same dystrophinopathy but a milder phenotypic expression (*i.e.* BMD), it showed lower SNIP and VC in DMD from the ages of 6.2 and 9.1 years, respectively. It appears that the longitudinal assessment of SNIP, which is a direct indicator of respiratory muscle function, was the earliest marker of inspiratory muscle strength

decline in our young DMD children. SNIP measurement, obtainable from DMD subjects as young as 5 years, could be suitable as a sensitive secondary outcome measure specifically evaluating respiratory muscle strength in children up to 10 years of age. SNIP may also provide information regarding the severity of the clinical DMD subphenotype, as children requiring earlier NIV exhibit an earlier decrease in SNIP (fig. 5).

Maximal inspiratory pressure

This study included DMD children from a younger age (5 years) than previous studies [4, 7]. Our P_{Imax} results, showing no significant evolution of P_{Imax} from 5 to 20 years of age, are in agreement with another longitudinal study [5] but differ from a transverse study showing a P_{Imax} increase from 7 to 14 years of age followed by a decrease in 15–18-year-old DMD patients [27].

Vital capacity

Our study showed that the VC of DMD children increases until 12.5 years of age (reaching maximum predicted value of 1.82 L) and then decreases. These results are consistent with those of studies evaluating the age-related change in VC in DMD patients longitudinally [5, 6] but again differ from those of the transverse study by HAHN *et al.* [27]: the higher VC peak (2.66 L, SD 0.87 L) in their 13–14-year-old DMD patients could be explained by a more favourable DMD subphenotype (data concerning ages at loss of ambulation in that population were not provided). The cross-sectional design of the study by HAHN *et al.* [27] may also have decreased the accuracy of assessment of individual pattern of age-related changes of pulmonary function of DMD patients [28, 29].

Strengths of our study

Due to our longitudinal study design and the use of a statistic analysis adapted to the longitudinal assessment of data (online supplementary material), this study was able to accurately describe the age-related pressure and volume changes in DMD children.

Respiratory muscle tests compared with the gold standard VC

Presently, respiratory function in patients with DMD is monitored by routine measurement of VC [18], an indicator of both respiratory muscle function and lung and chest wall compliance. SNIP measurement should be used in young patients with neuromuscular disorders for detecting respiratory weakness. Firstly, most children from the age of 5 years are able to perform adequate SNIP tests whereas a few children with neuromuscular disorders are unable to perform acceptable and repeatable VC manoeuvres [8]. Secondly, our study showed that the SNIP measurement detects the respiratory muscle weakness of DMD children earlier than VC. Finally, comparing the age-related change in SNIP and VC in DMD patients to those of BMD patients, it showed that low SNIP values are observed at an earlier age than low VC values in the DMD group. In patients with advanced restrictive ventilatory defect secondary to neuromuscular disease, VC has, however, been described as a more sensitive marker of disease progression than maximum pressures [30].

Limitations of the study

We did not evaluate the expiratory muscle strength that also contributes to the VC but maximal expiratory pressure measurements cannot usually be obtained in subjects <7 years of age [30]. It would have been interesting to see whether this differs in BMD *versus* normal subjects, and how much difference there is between healthy controls and DMD patients, but we considered it infeasible to conduct such a 3-year study in healthy children.

Conclusion

In conclusion, the design of our study allowed accurate assessment of the change in three parameters of pulmonary function over 3 years in BMD and DMD patients. It emphasised the age-related pressure and volume differences between these conditions, *i.e.* increases in SNIP, P_{Imax} and VC from 5 to 20 years of age in BMD *versus* a SNIP decline from the age of 10.5 years, no change in P_{Imax} and a VC decline from 12.5 years in DMD. In particular, significantly different age-related changes are shown in DMD compared with BMD, with SNIP values being lower from an earlier age than P_{Imax} or VC. However, the SNIP and P_{Imax} tests are complementary [24] and should be used in combination with VC for a complete sequential assessment of inspiratory muscle strength in patients with neuromuscular disease. Our study shows that SNIP is superior to P_{Imax} in children up to 10 years of age and that SNIP is much more feasible and more repeatable than P_{Imax}, and it suggests that SNIP is useful in the detection of inspiratory strength decline in young DMD cases when VC values remain within normal values. Baseline PFTs should be performed early in the course of the disease, between 4 and 6 years of age (American Thoracic Society consensus statement

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[18]) and sitting FVC should be obtained in ambulatory DMD children ⩾6 years of age [31]. Therefore, in clinical care, we propose: 1) that longitudinal assessment of SNIP should be initiated early in the course of the disease, from 5 years of age; and 2) when a SNIP decline is observed, that additional measures of pulmonary function (including VC) and gas exchange should be assessed in order to determine the need for intensified therapy. In research, as SNIP longitudinal assessment is reliable and feasible in nearly all patients >5 years of age and as it is able to detect the beginning of the respiratory disease, we propose to use SNIP longitudinal assessment as a physiological outcome measure in clinical trials for emerging therapeutics for young DMD patients from the age of 5 years.

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