Earlier decline in sniff nasal inspiratory pressure than peak expiratory flow in children with Duchenne muscular dystrophy

To the Editor:

In Duchenne muscular dystrophy (DMD), progressive weakness of the respiratory muscles leads to a restrictive ventilatory defect contributing to early morbidity and mortality. We have recently shown by a longitudinal assessment of vital capacity and sniff nasal inspiratory pressure (SNIP) in young DMD children that SNIP was an earlier marker of decline in respiratory muscle strength than vital capacity [1]. However, early involvement of the expiratory muscles is a characteristic feature of DMD, as shown by the earlier decrease in expiratory ($P_{\text{Emax}}$) than inspiratory maximal pressure ($P_{\text{Imax}}$) [2]. In the absence of bronchial obstruction, peak expiratory flow (PEF) reflects maximal expiratory muscle strength [3]. In patients with respiratory weakness, PEF is reduced and correlated with $P_{\text{Emax}}$ [4]. Recently, it was shown that DMD patients on a 1-year idebenone treatment improved in expiratory muscle strength (evaluated by PEF) while patients on placebo deteriorated [5]. No difference between treatments groups were observed for measures such as vital capacity [6], suggesting that PEF could be used as an outcome parameter to assess the effect of early therapeutic interventions on respiratory muscle strength in DMD. As candidate drugs for the treatment of DMD enter clinical trials, it is important to determine the natural evolution of pulmonary function parameters that could be used as outcome measures for efficacy studies in DMD children. However, to our knowledge, there are no data on the natural evolution of PEF in young DMD children and there is no information on the age of PEF decline compared with the age of SNIP decline. Therefore, we aimed to assess the PEF and SNIP change with age in glucocorticoid-naïve DMD children in order: 1) to document the natural evolution of PEF measurement; and 2) to identify the ages of decline in PEF and SNIP in DMD children.

A 3-year, prospective follow-up of SNIP and PEF at 6-month intervals was performed in 33 DMD, steroid-naïve 5–20-year-olds [1]. Vital capacity and $P_{\text{Imax}}$ were also assessed [1].

Inclusion criteria and SNIP assessments have been described previously [1]. At least 10 (most often 15–20) maximal sniffs, performed from functional residual capacity, were obtained. PEF was obtained from flow-volume curve data (Masterscreen Pneumo; Erich Jaeger, Wurzburg, Germany) as the maximum expiratory flow achieved from a maximum forced expiration, starting without hesitation from the point of maximal lung inflation. The largest value from at least three acceptable manoeuvres was recorded [7]. Results were expressed as z-scores [8, 9]. Median (interquartile range (IQR)) is presented for continuous variables and percentages for categorical variables. At inclusion, for SNIP, the within-session repeatability was evaluated by the coefficient of variation (CoV), and for PEF, by the difference between the largest and the next largest manoeuvre [7]. A nonlinear mixed model was used to analyse the change of PEF and SNIP versus a broken function of age that took 0 before the knot and subject’s age after the knot [10]; the knot position was optimised by the smallest Akaike information criterion. At this optimal knot, intercept (no change) and slope (decrease) was estimated; comparison between the age of the knot for SNIP and that for PEF was performed on the z-score value of these two parameters.

The full DMD characteristics were described in our previous study; ambulation was lost at a median age of 9.4 years (IQR 8.3–10.4 years). Scoliosis developed in 61% of DMD during the follow-up; spine fusion was performed in 36% of the non-ambulatory patients with spinal curvature $\geq 30^\circ$ at a median age of 13.2 years (IQR 12.5–13.8 years). Nocturnal non-invasive ventilation (NIV) had been initiated in one subject before the beginning of the study.

At inclusion, median age was 11.0 years (range 5.0–16.7 years), median height was 136 cm (range 103–170 cm) and median body mass index (BMI) z-score was -0.10 (range -4.80–6.30) [11]. Baseline median SNIP z-score was -2.20 (range -4.24– -0.91; 79% of children had values $< -1.64$) while baseline median PEF z-score was -1.20 (range -3.94–0.58; 34% of children had values $< -1.64$).
8% (IQR 6–11%). Median difference between the largest two PEFs was 0.050 L $\cdot$ s$^{-1}$ (IQR 0.040–0.190 L $\cdot$ s$^{-1}$) or 2% of highest PEF (IQR 1–6%).

The model (broken function of age) that best fitted SNIP and PEF values in longitudinal analysis is shown in figure 1, demonstrating an earlier decline in SNIP than PEF values (from 9.72 years of age (95% CI 8.89–10.55 years) and 11.45 years of age (95% CI 11.09–11.81); p<0.0001).

Although early involvement of the expiratory muscles is a characteristic feature of DMD (as shown by the earlier decrease in $P_{\text{Emax}}$ than $P_{\text{Imax}}$ [2] or values of gastric pressure during cough being below normal values in patients as early as 8 years of age [12]), this longitudinal assessment of SNIP and PEF shows an earlier decline in SNIP than PEF in DMD children.

PEF baseline values in the present study showed a good repeatability (as the largest two blows were reproducible to within 0.670 L $\cdot$ s$^{-1}$ [7] and as median difference between the two best measurements was 2% of the best) and appeared reliable. Our transverse data at inclusion showed that a significant decrease in inspiratory muscle pressure (SNIP z-score $<-1.64$) was already present in a majority (79%) of children (median age 11 years) while only a minority them (34%) of experienced a significant PEF decrease. As a result, median SNIP was already below normal values (z-score -2.20) while median PEF remained within normal values.

Our longitudinal data analysis adds that the decline in SNIP values began 1.73 years earlier than that of PEF. As PEF depends not only on expiratory strength but also on inspiratory effort [13], we suggest that PEF may be relatively preserved as long as the inspiratory muscle function, the speed of inspiration (as evaluated by SNIP), the vital and inspiratory capacities, and the thoracopulmonary elastic recoil are only moderately affected [14]. We also suggest that with deterioration of both inspiratory muscle strength and vital capacity, after 11 years of age (the same broken-line model applied to the longitudinal assessment of vital capacity showed that vital capacity values were below the lower limit of normal after 11 years of age), DMD subjects may no longer be able to perform fast inspirations reaching 85–95% of their inspiratory capacity, producing increases in the elastic recoil of the lung and chest wall and, therefore, greater PEF values, and enhancing expiratory muscle pressure during the subsequent expiration [15].

SNIP is useful in the detection of inspiratory strength decline in young DMD cases when vital capacity remains within normal values. It has the advantage of being obtainable from DMD subjects as young as 5 years and could be suitable as a sensitive secondary outcome measure specifically evaluating respiratory muscle strength in young 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 [1].

In conclusion, although PEF was shown to be a sensitive parameter to monitor the effect of therapeutic intervention on respiratory muscle strength in 8–16-year-old DMD children [6], our data show that SNIP decline occurred before PEF decline in young DMD children and that SNIP decline is therefore an earlier sign of the decline of respiratory muscle strength in DMD than the decline of PEF.

Earlier decline in SNIP than PEF was observed during follow-up of Duchenne muscular dystrophy children http://ow.ly/zbr6a
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References