Evolution of Respiratory Function in Duchenne Muscular Dystrophy from Childhood to Adulthood

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ON LINE SUPPLEMENT

Statistical data analysis

We used a basis of S natural cubic splines built on the time domain 6-24 years, where $S = 5$ was chosen by minimizing the PRESS index (i.e., predictive residual error sum of squares) which is a leave-one-out cross-validation estimate of the average squared prediction error of the fitted model when it is used to predict the value of unobserved data.

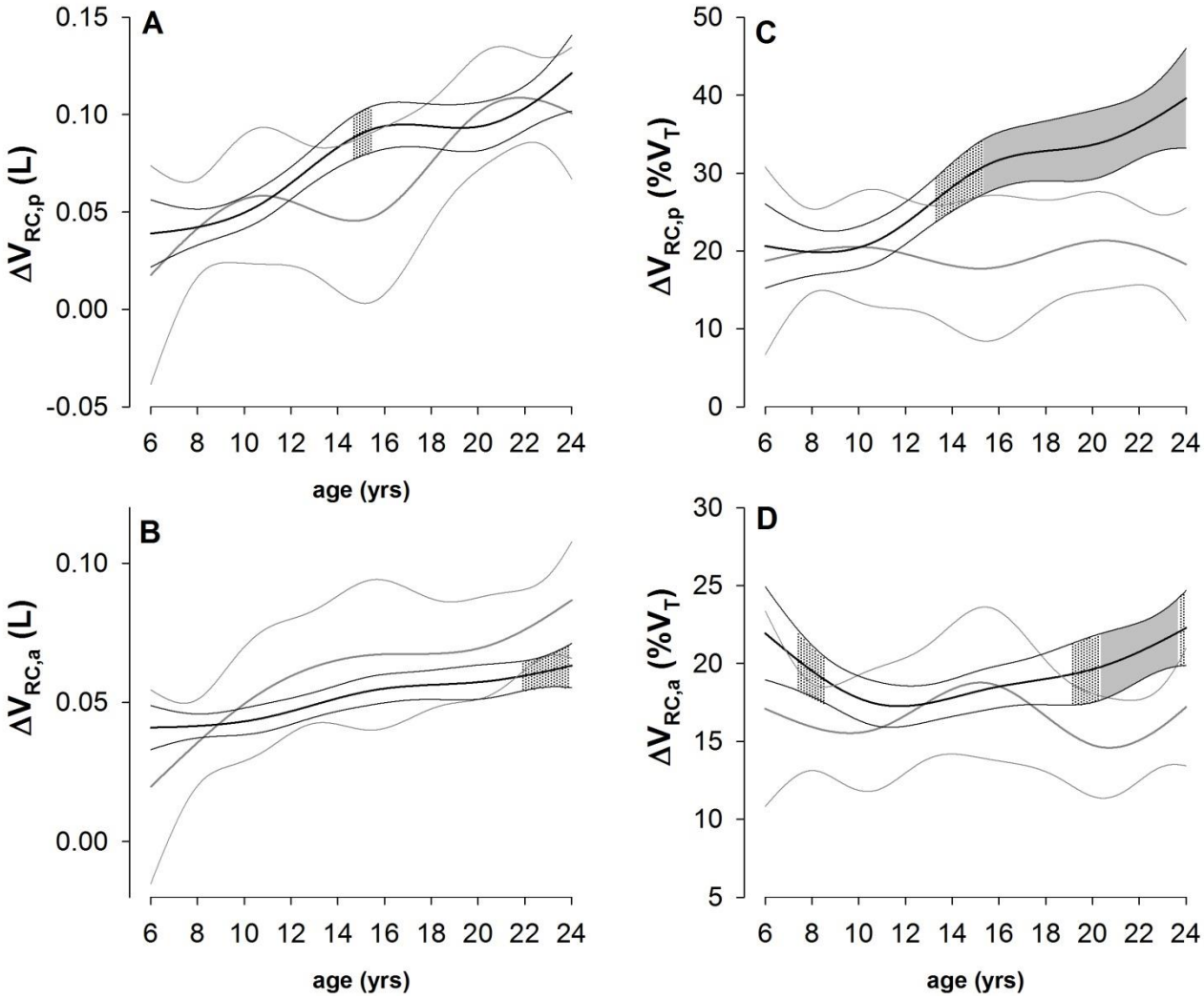
In detail, $\phi_k(t)$ is the value at age t of the k-th natural cubic spline ($k = 1, \dots, S$), β_{kG} is the regression coefficient related to ϕ_k and to the group G, b_{kiG} is the random regression coefficient related to ϕ_k and to the i-th subject in the group G, and $\varepsilon_{iG}(t)$ is the measurement error at age t related to the i-th subject in the group G. We assumed that $b_{kiG} \sim \mathcal{N}(0, \sigma_k^2)$ for each subject i in the group G, allowing a different variance σ_k^2 for each natural cubic spline, and that the measurement errors $\varepsilon_{iG}(t) \sim \mathcal{N}(0, \sigma^2)$ for each subject i in the group G for every time t. Moreover, we assumed all random terms in the models to be independent.

For every acquired datum of the subjects, we computed by maximum-likelihood estimation the population mean curve $\mu_{TOT_G}(t) = \sum_{k=1}^{S} \beta_{kG} \phi_k(t)$ for each time $t \in (6,24)$ and group G, and its 95% pointwise asymptotic confidence intervals. In addition, we performed asymptotic likelihood-based tests to find whether and at which age t there was a significant difference the mean curve of a

specific group *G* and to the mean curve of another group (or with respect to a known reference curve). Within this procedure, we identified three settings:

1. when considering $y_{iG}(t)$ as the percentage of predicted value of a parameter (i.e. FVC, FEV_1, ΔV_{AB}), we used "100%" as its reference value;
2. when considering $y_{iG}(t)$ as one parameter of the breathing pattern in its original unit of measure, we compared the mean curve of the DMD patients to the mean curve of the control population;
3. instead, when considering $y_{iG}(t)$ as one parameter of the spirometric test in its original unit of measure, first we computed the pairwise difference between the ideal and the observed values of each subject; then we constructed the population mean curve of these differences with the model (1) and we tested whether and at which age *t* the resulting mean curve is significantly non-zero.

Figure



Evolution with age of the maximum-likelihood estimation population mean curve (thick line) and its 95% pointwise asymptotic confidence intervals (thinner lines) of pulmonary ribcage volume variations ($\Delta V_{RC,p}$) and abdominal ribcage volume variation ($\Delta V_{RC,a}$) expressed in liters (A and B, respectively) and as percentage contribution to tidal volume (C and D, respectively) during spontaneous breathing in supine position in DMD patients (black lines) and in healthy controls (grey lines). Dotted areas: values significantly different from predicted with $0.05<p>0.01$. Grey areas: values significantly different from predicted with $p<0.01$.