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Supine changes in lung function correlate with chronic respiratory failure in myotonic dystrophy patients

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ABSTRACT

Quality of life and prognosis of patients with myotonic dystrophy type 1 (MD1) often depend on the degree of lung function impairment. This study was designed to assess the respective prevalence of ventilatory restriction, hypoxaemia and hypercapnia in MD1 patients and to determine whether postural changes in lung function could contribute to the early diagnosis of poor respiratory outcome.

Fifty-eight patients (42.6 ± 12.9 years) with MD1 were prospectively evaluated from April 2008 to June 2010 to determine their supine and upright lung function and arterial blood gases.

The prevalence of ventilatory restriction was 36% and increased with the severity of muscular disability (from 7.7% to 70.6%). The prevalence of hypoxaemia and hypercapnia was 37.9% and 25.9%, respectively. Multiple regression analysis showed that the supine fall in FEV_1 was the only variable associated with ventilatory restriction, hypoxaemia and hypercapnia.

Our data indicate that supine evaluation of lung function could be helpful to predict poor respiratory outcome, which is closely correlated with hypoxaemia and/or hypercapnia.

1. Introduction

Myotonic dystrophy Type 1 (MD1, Steinert's disease) is one of the most common muscular dystrophies in adults, with a prevalence of 3–15/100,000 in Europe (Harper, 2001). MD1 is an autosomal dominant multisystem inherited disorder related to expansion of a trinucleotide (CTG) repeat in exon 15 of the 3′-untranslated region of the myotonic dystrophy protein kinase gene on chromosome 19q13.3. The disease has a progressive course, comprising muscle weakness, wasting and myotonia (Kaminsky and Pruna, 2012). Respiratory dysfunction is common, involving ventilatory restriction and alveolar hypoventilation. The quality of life and prognosis of these patients vary according to the degree of lung function impairment (Kaminsky et al., 2011, 2013). However, the time-course of impaired respiratory function has not been clearly defined. More importantly, factors predictive of poor respiratory outcome have not been identified, therefore making it difficult to establish the prognosis early in the course of follow-up.

In other neuromuscular disorders, especially amyotrophic lateral sclerosis (ALS), postural spirometry has been recommended to improve the detection of diaphragmatic involvement (Fromageot et al., 2001; Perez, 2006; Wallgren-Pettersson et al., 2004) and some authors have suggested that the supine fall in forced vital capacity could be used as a marker to initiate noninvasive positive pressure ventilation and to predict respiratory symptoms (Varrato et al., 2001).

This study, conducted in a sample of ambulatory MD1 patients, was designed to determine whether postural changes in spirometry could contribute to the early diagnosis of impaired respiratory function.

2. Materials and methods

2.1. Subjects and experimental protocol

All ambulatory adult patients (18 years of age and older) with a clinical diagnosis of myotonic dystrophy type I referred to the department of "Internal Medicine and Orphan Diseases" were prospectively investigated as part of routine follow-up from April 2008 to June 2010. Patients were evaluated clinically by an internist (P. Kaminsky or L. Pruna) in this department and lung function

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was assessed in the "Pulmonary Function Testing" department of Nancy University Hospital (France). Pulmonary function tests were carried out according to clinical indications, and not as part of a study protocol. Supine evaluation was added to conventional lung function testing. All individuals were classified by the same physician (P. Kaminsky) according to a standardised five-point muscular impairment rating scale, in which a score of 1 indicated no muscular impairment, a score of 2 indicated minimal signs without distal weakness except for digit flexors, a score of 3 indicated distal weakness without proximal weakness except for elbow extensors, a score of 4 indicated moderate proximal weakness, and a score of 5 indicated severe weakness (MIRS) (Mathieu et al., 2001). All assessments were performed during a 1- to 3-day hospitalisation. Patients needing noninvasive ventilation were excluded from the study, in order to focus on the early phases of the disease and to more accurately assess the first signs of respiratory dysfunction. The CTG repeat sequence was analysed on leukocytes by polymerase chain reaction assays and analysis of restriction fragment length polymorphisms, and the Southern blot technique (Brook et al., 1992; Fu et al., 1992). The study was approved by the Nancy University Hospital Local Ethics Committee and informed consent was obtained from all subjects before participation.

All pulmonary function tests (including spirometry, respiratory muscle strength and arterial blood sampling) were performed in a single session for each patient. Physical examinations and pulmonary function assessment were performed within an interval of 2 days.

2.2. Lung and respiratory muscle function

All pulmonary function tests met appropriate standards of the European Respiratory Society/American Thoracic Society (Miller et al., 2005).

Spirometry and plethysmography were performed in the upright seated position and were systematically associated with spirometry in the supine position (in random order). Data were compared with the predicted normal values obtained by the European Coal and Steel Community and expressed as a percentage of the normal value (Quanjer et al., 1993). In the absence of reference standards, percentages of predicted supine values were calculated using predicted values for the upright position. The flow/volume curve and lung volumes were assessed by open-circuit spirometry and plethysmography, respectively (Vmax – Autobox V62J Encore, SensorMedics, Yorba Linda, CA). Ventilatory restriction was defined as both VC and TLC <80% of predicted.

Voluntary Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP) were both measured in the seated position using a standard flanged mouthpiece. A small leak in the mouthpiece prevented contribution of the orofacial muscles. MIP was measured from Residual Volume (RV) and MEP was measured from Total Lung Capacity (TLC), both according to standard techniques (Troosters et al., 2005). The procedures were repeated at least three times and the best value was recorded (Troosters et al., 2005). When appropriate, respiratory muscle strength (RMS) was used, defined as the mean of MIP and MEP expressed as a percentage of predicted values (Uldry and Fitting, 1995).

2.3. Arterial blood sampling and blood gas analysis

Arterial blood gases were drawn at rest (before spirometry) from the radial artery of the nondominant arm while the patient was comfortably seated for 10 min. A sterile, self-filling and disposable pre-heparinized system was used to take 1.5 ml of arterial blood (DRIHEP Plus, Vacutainer Systems, Becton Dickinson, USA).

Arterial oxygen partial pressure (PaO_2) and arterial carbon dioxide partial pressure ($PaCO_2$) were determined within 10 min after sampling (ABL 800, Radiometer, Copenhagen, Denmark). Room temperature and barometric pressure were used daily to adjust calibrations and measurements. Quality control of blood-gas equipment was performed twice daily.

The alveolar–arterial oxygen pressure gradient ($P(A\text{-}a)O_2$) was estimated using the following equation (Fenn et al., 1946):

$$P(A\text{-}a)O_2 = (FIO_2 \times (Pb - 47) - (PaCO_2/0.8)) - PaO_2$$

where FIO_2 is the fraction of inspired oxygen; Pb is the barometric pressure at sea level and pressures are expressed in mmHg.

Hypercapnia was defined as $PaCO_2 > 45$ mmHg and hypoxaemia as $PaO_2 < 80$ mmHg.

2.4. Statistical analysis

Data were expressed as mean ± standard deviation. Groups were compared by Fisher's exact test for qualitative variables and Kruskal–Wallis test for quantitative variables. Correlations were investigated by using least-square linear regression techniques. Univariate analysis was used to assess the independent contribution of each variable. A full model, stepwise, multiple, linear regression analysis was then performed to determine the influence of each variable. The level of significance was set at 5%.

Sensitivity, specificity, positive predictive value and negative predictive value of significant variables to predict poor respiratory outcome (i.e. ventilatory restriction, hypercapnia and hypoxaemia) were determined at the same assessment. Repeated receiver operating characteristic (ROC) analysis was applied to calibrate cut-off values for variables of interest. These cut-points were identified by optimising the area under the ROC curve.

3. Results

3.1. Patients

Fifty-eight ambulatory MD1 patients with a mean age of 42.6 ± 12.9 years (35 females, 23 males) were investigated. Patients were classified according to the MIRS: 8 patients in grade 1, 18 patients in grade 2, 15 patients in grade 3, 16 patients in grade 4 and only one patient in grade 5, as shown in Table 1. Grades 1 and 2 and grades 4 and 5 were pooled for further statistical analysis. No statistically significant differences were observed between the MIRS groups in terms of anthropometric data, but patients with proximal weakness tended to be older with higher BMI and longer medical follow-up.

3.2. Lung function

Spirometric, blood gas and respiratory muscle strength data for each MIRS group are shown in Table 1. Fig. 1 illustrates the relationship, albeit weak, between the decline of VC and the level of respiratory muscle weakness, evaluated by measurement of voluntary maximal respiratory pressures. Table 2 shows the same data as in Table 1, but expressed for two groups: with and without ventilatory restriction. Twenty-one patients (36.2%) presented a restrictive ventilatory pattern and were found to be overweight ($p = 0.0026$), with a higher BMI ($p = 0.0256$), a greater number of CTG triplet repeats ($p = 0.0195$) and more pronounced muscular disability ($p < 0.0001$). They were also more hypoxaemic ($p = 0.0310$) and hypercapnic ($p = 0.0238$). No linear relationship was observed between PaO_2 and FVC in the sitting position, but a significant positive correlation was observed between PaO_2 and the supine fall in FVC ($p = 0.0028$, $r^2 = 0.15$) and also with the supine fall in FEV_1 (forced expiratory volume in one second) (see Fig. 2, $p = 0.0023$, $r^2 = 0.15$).