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# Respiratory muscle dysfunction in facioscapulohumeral muscular dystrophy

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**Abstract**

Respiratory insufficiency in facioscapulohumeral muscular dystrophy has rarely been studied. We compared two age- and sex-matched groups of 29 patients, with and without respiratory dysfunction. Tests in the 29 patients with respiratory dysfunction suggested predominant expiratory muscle dysfunction, leading to ineffective cough in 17 patients. Supine and upright vital capacities were not different ($P = 0.76$), suggesting absence of diaphragmatic dysfunction. By stepwise regression, only expiratory reserve volume correlated with the Walton and Gardner-Medwin score ($R^2 = 0.503$; $P = 0.001$). Compared to controls, patients with respiratory dysfunction had higher values for the Walton and Gardner-Medwin score ($6.1 \pm 1.9$ vs. $3.2 \pm 1.2$; $P < 0.0001$) and body mass index ($26.9 \pm 6.0$ vs. $22.9 \pm 4.0$ kg/m$^2$; $P = 0.003$) and a smaller number of D4Z4 allele repeats ($4.8 \pm 1.6$ vs. $5.7 \pm 1.8$; $P = 0.05$). Mechanical ventilation was required eventually in 20 patients, including 14 who were wheelchair bound. Three patients had acute respiratory failure requiring mechanical ventilation; 16 patients had poor airway clearance, including 10 with sleep apnea syndrome, responsible in 7 for chronic hypercapnia. Two patients presented isolated severe sleep apnea syndrome. Respiratory dysfunction in facioscapulohumeral muscular dystrophy is predominantly related to expiratory muscle weakness. Respiratory function and cough effectiveness should especially be monitored in patients with severe motor impairment and high body mass index.


*Keywords:* Respiratory failure; Facioscapulohumeral muscular dystrophy; Pulmonary function tests; Mechanical ventilation; Neuromuscular respiratory dysfunction

## 1. Introduction

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant disorder and the third most common hereditary muscle disease in adults. The first symptom of this slowly progressive myopathy is facial weakness, which is followed by dysfunction of the shoulder girdle muscles. Clinical severity varies widely, and patients may remain able to walk or become dependent on a wheelchair [1,2]. Sleep-disordered breathing (SDB) [3–5] and swallowing dysfunction [6] due to upper airway muscle dysfunction have been described. However, respiratory dysfunction is considered rare in FSHD, despite some reports of respiratory failure [7,8]. In a nationwide Dutch study [8] investigating the prevalence of respiratory insufficiency in FSHD, only 1% (10 patients) of all FSHD patients were receiving home mechanical ventilation (MV). All of them were wheelchair bound and 9 had vital capacity (VC) values below 50%. Similarly, in a 10-year prospective study, nearly half of the 53 patients with FSHD had restrictive lung disease but only 13% had severe respiratory dysfunction [9]. A third study suggested frequent involvement of both inspiratory and expiratory muscles in FSHD [7] but included only patients with normal VC and no risk of respiratory failure.

Here, our objective was to evaluate the frequency, characteristics, outcomes, and relationship with FSHD severity of respiratory dysfunction in patients with FSHD seen at our reference center for degenerative neuromuscular diseases. We designed a case–control study in which we compared patients

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with respiratory dysfunction to age- and sex-matched patients without respiratory dysfunction.

## 2. Materials and methods

The study was approved by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL), in accordance with French legislation.

### 2.1. Patients

Data were collected from adults with FSHD referred for respiratory function evaluation at the home ventilation unit of the Raymond Poincaré University Hospital (Garches, France), between March 2001 and July 2013. FSHD was diagnosed using the conventional Southern blot-based method, according to international criteria [10,11]. We recorded the following for each patient: method of diagnostic confirmation, i.e., D4Z4 allele repeat number; respiratory symptoms at the first visit; use of a wheelchair and/or locomotor function as evaluated using the Walton and Gardner-Medwin (WGM) score [12]; and age at loss of ambulation. Respiratory symptoms were classified as follows: none, dyspnea; SDB (such as daytime sleepiness, fatigue, or morning headaches); and dyspnea plus SDB. Because our patients with FSHD were referred to our center by the Myology Institute of the Pitié-Salpêtrière Hospital (Paris, France), we selected control patients with no suspected respiratory dysfunction from the same institute: for each patient referred to us for lung function testing, we randomly selected an age- and sex-matched control among the 673 other patients with FSHD (365 men) receiving follow-up during the same period at the referring Myology Institute. The investigator was blinded to all patient information except the FSHD diagnosis, age, and sex. We collected the following data in the control group: WGM score, body mass index (BMI), VC (% predicted), smoking history, and number of D4Z4 allele repeats.

### 2.2. Lung function testing at the Raymond Poincaré Hospital

Lung function testing was performed according to ATS/ERS recommendations [13] using a Vmax 229 Sensormedics System (Yorba Linda, CA, USA) with the patient in the upright position [14]. VC was also measured in the supine position.

Maximal sniff nasal inspiratory pressure [15,16] and maximal inspiratory pressure (MIP) were measured from the functional residual capacity in the upright position. Maximal expiratory pressure (MEP) was measured at total lung capacity. For each parameter, the best value was recorded [17,18]. MIP and MEP were also expressed as the percentage of the estimated lower limit of normal [19]. As peak cough flow (PCF) is greater than or equal to peak flow [20], it was measured only when peak flow was below 270 L/min. PCF was measured using a well-fitted facemask (Leadal Medical, Limonest, France) instead of a mouthpiece, placed around the mouth to allow mouth opening and to minimize cheek compliance. Care was taken to avoid leaks around the mask. Patients were asked to cough as hard as possible, and the highest PCF obtained from three cough maneuvers, within 10% of the maximal value, was recorded. PCF cutoff values of 270 L/min and 160 L/min were used to detect cough disorders, as they are considered indicative of possible respiratory failure development during respiratory tract infections and of ineffective airway clearance, respectively [21].

In nonventilated patients, the initial evaluation included arterial blood gas measurements at rest and in the upright position, and nocturnal $SpO_2$ recording (OhmedaBiox, BOCHealthcare, Boulder, CO, USA). Polysomnography was performed in patients with suspected SDB [22].

After the first evaluation, noninvasive MV was recommended according to published criteria (VC ≤ 50% predicted in the upright position and/or $PaCO_2$ ≥6 kPa and/or $SpO_2$ ≤ 88% for at least 5% of total sleep time) [23].

### 2.3. Statistics

Data are described as number of patients and percentage of theoretical values when available. To compare inspiratory to expiratory muscle performance, we assessed potential correlations linking inspiratory capacity (IC) to expiratory residual volume (ERV) and MIP to MEP. In addition, we sought correlations between spirometry results and the WGM score [12]. Supine VC was compared to upright VC using correlation analysis and the *t*-test.

To identify potential associations linking respiratory function and BMI to FSHD severity or progression, we assessed whether daytime and nocturnal respiratory parameters and BMI correlated with the WGM score or the time from loss of ambulation to MV initiation. Results in females and males were compared using the unpaired *t*-test.

We evaluated the comparability of the groups with and without respiratory dysfunction based on VC (% predicted), smoking history, WGM score, BMI, and D4Z4 allele repeat number. A standard two-tailed *t*-test (and a chi-square test with Yates' correction for smoking history) was performed to compare the two groups.

Simple correlations were evaluated using the least-square linear regression technique. When necessary, a full, stepwise, multiple linear regression model was built to determine the influence of each variable.

The level of significance was set at 5%. Statistical tests were run using the StatView 5 package (SAS Institute, Grenoble, France).

## 3. Results

### 3.1. First visit

We obtained data from 29 patients with FSHD (11 males) and respiratory dysfunction (Table 1). FSHD was confirmed by genetic testing in all patients. The number of D4Z4 allele repeats was not available for 2 patients (#6 and #14).

The 29 patients had a mean age of 50.7 ± 14.8 years. Among them, 20 (68%) had BMI values >24 kg/m$^2$ and 10 were obese (BMI >30 kg/m$^2$) [24]. There were 17 patients (58%) who used a wheelchair. These patients had WGM scores ≥7 and a mean age at loss of ambulation was 42.8 ± 23.4 years. Mean time from loss of ambulation to MV initiation was 12.2 ± 10.8 years. VC was <50% of predicted in 14 (48%) patients (Table 1). Total

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