The influence of body composition on respiratory muscle, lung function and diaphragm thickness in adults with cystic fibrosis

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Received 17 July 2006; received in revised form 15 November 2006; accepted 27 February 2007
Available online 2 April 2007

Abstract

Background: Weight loss and loss of fat-free mass (FFM) are associated with peripheral muscle wasting in cystic fibrosis (CF) although whether this co-exists with loss of diaphragm mass remains unclear.

Methods: FFM was determined by dual-energy X-ray absorptiometry and bioelectrical impedance in 40 adults with CF and 30 age-matched healthy subjects (HS). Diaphragm thickness at functional residual capacity (FRC) [TDIrel] and total lung capacity (TLC) [TDIcont] and thickening ratio (TR) were assessed by ultrasonography. Inspiratory muscle strength and work capacity were determined by maximal inspiratory pressure (PImax), and sustained PImax (SPImax); pulmonary function (RV, VC and TLC) and physical activity status (PAS) were also determined.

Results: When the CF patients were assessed as a group (low and normal FFM) they had similar age, weight, height and PAS compared to the HS, although patients had lower FFM (p<0.05), VC and TLC than the HS (p<0.01). In addition, although PImax, TDIrel, TDIcont and TR were similar between the patients and the HS, SPImax was lower in the patients (p<0.01). When analyses were made between patients with low versus normal FFM and between patients with low FFM and HS no significant differences were found between overall weight although TDIrel, TDIcont, TR and PAS were all reduced in patients with low FFM (p<0.01).

Conclusions: PImax is relatively well preserved in adults with CF although there is a relationship between the loss of inspiratory muscle work capacity, FFM, PAS and pulmonary function. Furthermore loss of FFM is associated with loss of diaphragm muscle mass.

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Keywords: Body composition; Diaphragm thickness; Cystic fibrosis

Abbreviations: BMI, body mass index (kg/m²); CF, cystic fibrosis; CRP, C-reactive protein (μg/ml); DXA, dual-energy X-ray absorptiometry; FEV1, forced expiratory volume in 1 s (% predicted); FFM, fat-free mass (kg); FRC, functional residual capacity (litres); HS, healthy subjects; PAS, physical activity status (MET’s); PImax, maximal inspiratory pressure (cm H2O); RV, residual volume (litres); SPImax, sustained maximal inspiratory pressure (pressure/time units); TDIcont, diaphragm thickness measured by ultrasound at total lung capacity (mm); TDIrel, diaphragm thickness measured by ultrasound at functional residual capacity (mm); TR, thickening ratio (%); TLC, total lung capacity (litres); VC, vital capacity (litres).

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doi:10.1016/j.jcf.2007.02.006
1. Introduction

Growth retardation and undernutrition are often seen in patients with cystic fibrosis (CF) as a result of several factors including malabsorption [1,2], reduced energy intake [3], increased energy expenditure [4,5] and the inflammatory state secondary to chronic pulmonary infection [6]. Such events lead to loss of fat mass and fat-free mass (FFM). The loss of FFM leads to a reduction in skeletal muscle mass that may co-exist with inspiratory muscle wasting and loss of inspiratory muscle function [7,8]. Furthermore patients with low FFM have been shown to have low levels of physical activity [9] and muscle function [7,8]. Furthermore patients with low FFM leads to a reduction in skeletal muscle mass that may co-

lead to loss of fat mass and fat-free mass (FFM). The loss of fat mass, FFM remains unclear. Indeed it has been suggested that diaphragm bulk is maintained in CF [11], even in the face of peripheral muscle atrophy [12]. The most widely held hypothesis for this phenomenon is the presence of a training effect on the respiratory muscles [11,13] due to the loads imposed by chronic hyperinflation and increased work of breathing as indices of inspiratory muscle strength, measured by non invasive methods, appear to be well preserved in CF patients. However, the assessment of volitional techniques to measure muscle strength is especially sensitive to the level of effort exerted [14] and may therefore be strongly influenced by the subject’s ability and motivation. Also, the large intra subject variability of diaphragm thickness observed in some studies [11,12] indicates that the beneficial response to an increased workload on the inspiratory muscles does not occur in all CF patients. In addition, the different clinical profiles of the patients in terms of respiratory impairment and nutritional status make it difficult to interpret studies which have assessed diaphragm bulk [11,12].

The aim of this study was to investigate the effect of loss of fat-free mass on pulmonary function, physical activity and diaphragm thickness in patients with CF. In order to investigate these aims, patients with low versus normal fat-free mass were compared with a group of healthy age-matched controls. The relationships between fat-free mass, diaphragm thickness, physical activity status, lung function and indices of inspiratory muscle endurance were also determined.

2. Methods and materials

2.1. Subjects

Forty adult CF patients (22 males) with proven CF and 30 age-matched healthy subjects (15 males) were studied. Mean age of the patients was 22.4 (age range, 18–32 years); mean age of the healthy subjects was 21.7, (age range, 18–33 years) (Table 1). Patients were excluded from the study based on the following criteria: liver cirrhosis, cor pulmonale or an exacerbation of their respiratory symptoms (increased respiratory symptoms, weight loss, fever, or reduction in FEV1 of >10% than the usual value) or elevated C-reactive protein (> 15.5 µg/ml). None of the patients had obvious signs of malabsorption; all had pancreatic insufficiency and were taking supplementary pancreatic enzyme products with meals. All healthy subjects were non-smokers, had no evidence of pulmonary pathology (e.g. asthma) or were suffering from any known metabolic or endocrine disorder. An adequate sample size was found to be at least 10 subjects per group at α=0.05 and 1−β=90%. All subjects were informed of the nature of the study and gave full written consent prior to the study which had Research Ethics Committee approval.

2.2. Study design

This was an observational, cross-sectional study comparing 40 CF patients to 30 healthy subjects (controls). Following this analysis the CF patients were classified as having either severe (mean FEV1 36.7 and FFM 36.2 kg respectively) or moderate disease (mean FEV1 56.3 and FFM 53.0 kg respectively) and analysed separately with the controls. At the initial screening visits, in all patients and controls, body composition, pulmonary function and physical activity status were determined. In addition, all subjects had an assessment of their inspiratory muscle function and diaphragm thickness (Table 1). All measurements of these variables were obtained by persons who were blinded to the nature of the study.

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>CF patients (n=40)</th>
<th>Healthy subjects (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.4 (21.2–23.6)</td>
<td>21.7 (20.3–23.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 (160.1–171.9)</td>
<td>168 (164.4–171.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.2 (58.5–62.0)</td>
<td>64.4 (60.9–67.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.0 (21.0–23.0)</td>
<td>23.0 (22.2–23.8)</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>44.6 (38.6–50.6)</td>
<td>56.8 (49.8–63.8)*</td>
</tr>
<tr>
<td>PAS (MET’s)</td>
<td>37.0 (35.0–39.0)</td>
<td>41.5 (40.0–43.0)</td>
</tr>
<tr>
<td>FEV1 (% pred)</td>
<td>46.5 (46–47)</td>
<td>96.2 (95.2–97.2)*</td>
</tr>
<tr>
<td>VC (litres)</td>
<td>3.6 (3.3–3.9)</td>
<td>4.1 (3.7–4.5)*</td>
</tr>
<tr>
<td>RV (litres)</td>
<td>1.7 (1.6–1.8)</td>
<td>1.5 (1.4–1.6)</td>
</tr>
<tr>
<td>FRC (litres)</td>
<td>2.6 (2.2–3.0)</td>
<td>2.9 (2.6–3.1)</td>
</tr>
<tr>
<td>TLC (litres)</td>
<td>4.6 (4.2–5.0)</td>
<td>5.8 (5.6–6.0)*</td>
</tr>
<tr>
<td>Diaph (TDIrel) (mm)</td>
<td>2.8 (2.6–3.1)</td>
<td>3.4 (3.0–3.8)</td>
</tr>
<tr>
<td>Diaph (TDIcon) (mm)</td>
<td>3.9 (3.6–4.2)</td>
<td>4.4 (4.2–4.6)</td>
</tr>
<tr>
<td>TR (%)</td>
<td>2.7 (2.4–3.0)</td>
<td>2.9 (2.7–3.2)</td>
</tr>
<tr>
<td>PImax (cm H2O)</td>
<td>116 (109–123)</td>
<td>124 (119–129)</td>
</tr>
<tr>
<td>SPImax (PTU)</td>
<td>609 (543–675)</td>
<td>788 (733–843)*</td>
</tr>
</tbody>
</table>

Data are presented as mean (95% CI). FFM=fat-free mass. PAS=physical activity status (in MET’s (metabolic equivalents (1 MET=3.5 ml/kg/min))). TDIrel and TDIcont=diaphragm thickness at FRC (rel) and at TLC (cont). TR=diaphragm thickening ratio (%). PImax=maximum inspiratory pressure. PTU=pulse time units.

* p<0.01.
2.3. Body composition

Weight (kg) and height (cm) were determined using a stadiometer (cm) (accurate to 1.5 mm) (Holtain Ltd, Crosswell, UK) and an electronic balance (Mott electroscale, model LC 2424, UK). Body mass index (BMI) was calculated (kg/m²).

2.4. Dual energy X-ray absorptiometry (DXA)

In all CF whole body DXA scans (Hologic QDR200+, Hologic Inc Waltham, MA, USA) were performed 2 h before a meal and with an empty bladder. Subjects were scanned supine using a pencil beam mode, enhanced software, and a calculated radiation dose of 4.6 μSv. Each scan took 15–20 min. The coefficient of variation (CV) of the Hologic QRD 2000+ for whole body calculation was 0.4–1.0% [15]. FFM obtained from the healthy subjects was within the limits of a healthy UK population of the same age and sex, although these data were generated from bioelectrical impedance. Two groups of CF patients were defined according to FFM by DXA: (1) low FFM if less than the fifth percentile for the healthy subjects; (2) normal FFM if greater than the fifth percentile for the healthy subjects [16,17].

2.5. Diaphragm thickness

The coefficient of reproducibility (CR) of diaphragm thickness measured by ultrasound at functional residual capacity (FRC) (TDIrel) and TLC (TDIcont) was calculated from an examination of both within and between subject variations between measurements using analysis of variance models [18]. These were determined to be 90% and 91% respectively. In all subjects, diaphragm thickness (mm) was assessed by B-mode ultrasonography using a 7.5 MHz linear transducer (PLE 705S Toshiba Medical System, Japan) at the zone of apposition in either the eighth or the ninth intercostal space as described by De Bruin et al. [19]. In order to allow for possible alterations in lung volume due to gas trapping from an increase in airways resistance, the FEV1/FVC ratio was measured in order to determine that all measurements of diaphragm thickness were obtained at the same lung volume. The mean of three measurements was recorded by a single experienced reader. In order to standardise for any change in lung volume during these three estimations, the diaphragm thickening ratio (TR) was determined by the formulae of Ueki et al. [20].

2.6. Lung function

Three trials were conducted for each of the lung function measurements (FEV1, FVC and FEV1/FVC ratio) by dry wedge spirometry. The highest value was used as the representative score for each subject (Vitalograph Ltd., Bucks, UK); TLC, RV, RV/TLC, and FRC were obtained by helium dilution using a previously described wash-in technique [21].

2.7. Circulating C-reactive protein

Clinical stability was assessed by assessment of serum concentrations of C-reactive protein (CRP) which was determined by sandwich enzyme-linked immunosorbent assay with goat and rabbit anti-human CRP and anti-rabbit IgG-alkaline phosphatase conjugate [22] (Table 2).

2.8. Physical activity status

This was determined in all subjects using a recall questionnaire relating to physical activity in the preceding month. The activity score was expressed in METs (1 MET=the energy expended by a person at rest [1 MET=3.5 ml/kg/min]) [23].

2.9. Inspiratory muscle function

The coefficient of reliability (CR) values for measurements of maximum and sustained maximum inspiratory pressure (Plmax and SpImax) were previously established to be 89% and 90% respectively [24]. Plmax was determined using an electronic manometer and computer software. The manometer had a fixed leak via a 2 mm-diameter aperture that prevented glottal closure during the inspiratory manoeuvre [25] and set a maximum flow during the inspiratory effort proportional to the pressure achieved. The leak set a maximum during the inspiratory effort and allowed continuous measurement of pressure over a full range of lung volumes until no further pressure could be generated. This measure of work was termed sustained maximum inspiratory pressure (SpImax) [26]. The patient was asked to take a

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Body composition and physical activity scores for cystic fibrosis patients with low and normal fat-free mass (FFM) and healthy subjects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>CF patients low FFM (n=22)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>22.3 (20.7–23.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162 (158.0–166.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.6 (55.2–62.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.5 (20.7–22.3)</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>36.2 (29.2–43.2)</td>
</tr>
<tr>
<td>PAS (MET’s)</td>
<td>33.0 (29.9–36.1)</td>
</tr>
<tr>
<td>CRP (μg/ml)</td>
<td>7.5 (6.8–8.2)</td>
</tr>
</tbody>
</table>

* Data are presented as mean (95% CI). FFM=fat-free mass. PAS=physical activity status (in MET’s=metabolic equivalents [1 MET=3.5 ml/kg/min]). CRP=C-reactive protein.

† Patients with low FFM had significantly lower values in these variables than patients with normal FFM or healthy subjects.

‡ p<0.01.

§ p<0.05.

° Patients with normal FFM had significantly lower values in these variables than healthy subjects.
maximal and sustained inspiratory effort from residual volume (RV) to TLC, and pressure (cm H$_2$O) was recorded over time by a computer. PImax was the maximum pressure developed in the first second of inspiration; SPImax was measured as the area under the pressure–time curve [26].

### 2.10. Statistical analysis

Prior to all the analyses, normality of the data for all measured variables was assessed by the one-sample Kolmogorov–Smirnov test. Data not normally distributed were log$_{10}$ transformed. All data are presented as means and as 95% confidence intervals. Differences in the study group characteristics between the patients and healthy subjects were analysed using $t$-tests. Differences between patients with low versus normal FFM and healthy subjects were analysed using a one-way analysis of variance and post hoc Tukey tests. Relationships between variables were assessed using Pearson’s correlations. All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 12 and significance was set at $p<0.05$.

### 3. Results

#### 3.1. Body composition: patients compared with healthy subjects

When the 40 CF patients were expressed as a group (low and normal FFM) the patients had similar age, weight, height, physical activity status (PAS) and BMI compared to the healthy subjects, although the patients had lower values of FFM, FEV$_1$, VC and TLC ($p<0.01$). In addition to this, although PImax, relaxed and contracted diaphragm thickness (TDIrel and TDIcont) and thickening ratio (TR) were similar between the CF patients, the healthy subjects SPImax was found to be lower in the patients with CF ($p<0.01$) (Table 1).

### 3.2. Body composition: between patient comparisons

There were 18 patients with moderate disease (mean FEV$_1$ 56.3 and FFM 53.0 kg respectively) and 22 patients whose disease was categorised as severe (mean FEV$_1$ 36.7 and FFM 36.2 kg respectively). When analyses were made between patients within these categories, there were no significant differences found between age and weight although height, BMI, and PAS were all lower in the patients with low FFM (Table 2). Patients with a low FFM also had a reduced FEV$_1$ (% pred), VC ($p<0.01$), TLC ($p<0.05$) and a reduced PImax and SPImax ($p<0.01$). These findings were consistent with a reduction in both TDIrel and TDIcont ($p<0.01$) and (TR) ($p<0.05$) (Table 3).

### 3.3. Relationships between body composition, C-reactive protein, diaphragm thickness, and inspiratory muscle function in patients with cystic fibrosis

When the CF patients were analysed as a whole group (no separation for low versus normal FFM), there were significant positive correlations between height, and TDIcont ($p<0.05$) and TDIcont and BMI ($p<0.05$). TDIcont also correlated with PImax, SPImax and FFM ($p<0.01$). In addition to this, significant relationships were identified between SPImax and BMI ($p<0.05$) and SPImax and FFM and C-reactive protein ($p<0.01$). Lower levels of PAS were also shown to be

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>CF patients low FFM</th>
<th>CF patients normal FFM</th>
<th>Healthy subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$ (% pred)</td>
<td>36.7 (36.1–37.4)</td>
<td>56.3 (55.8–56.8)</td>
<td>96.2 (95.2–97.2)</td>
</tr>
<tr>
<td>VC (litres)</td>
<td>3.1 (2.9–3.3)</td>
<td>4.0 (3.8–4.2)</td>
<td>4.1 (3.2–4.5)</td>
</tr>
<tr>
<td>RV (litres)</td>
<td>1.8 (1.6–2.0)</td>
<td>1.6 (1.4–1.8)</td>
<td>1.5 (1.4–1.6)</td>
</tr>
<tr>
<td>TLC (litres)</td>
<td>4.1 (3.9–4.3)</td>
<td>5.1 (4.9–5.3)</td>
<td>5.8 (5.5–6.0)</td>
</tr>
<tr>
<td>FRC (litres)</td>
<td>2.5 (2.1–2.9)</td>
<td>2.8 (2.2–3.4)</td>
<td>2.9 (2.6–3.1)</td>
</tr>
<tr>
<td>Diaph (TDIrel) (mm)</td>
<td>2.5 (2.0–2.6)</td>
<td>2.7 (2.3–3.7)</td>
<td>3.4 (3.0–3.8)</td>
</tr>
<tr>
<td>Diaph (TDIcont) (mm)</td>
<td>3.3 (3.1–3.5)</td>
<td>3.9 (3.6–4.7)</td>
<td>4.4 (4.2–4.6)</td>
</tr>
<tr>
<td>TR (%)</td>
<td>2.4 (2.3–2.5)</td>
<td>2.8 (2.6–2.8)</td>
<td>2.9 (2.7–3.2)</td>
</tr>
<tr>
<td>PImax (cm H$_2$O)</td>
<td>109 (100–118)</td>
<td>119 (111–127)</td>
<td>124 (119–129)</td>
</tr>
<tr>
<td>SPImax (PTU)</td>
<td>520 (462–584)</td>
<td>698 (634–762)</td>
<td>788 (733–843)</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pearsons correlation coefficient ($r$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm) vs TDIcont (mm)</td>
<td>+0.273$^a$</td>
</tr>
<tr>
<td>Height (cm) vs SPImax (PTU)</td>
<td>+0.418$^b$</td>
</tr>
<tr>
<td>BMI (kg/m$^2$) vs TDIcont (mm)</td>
<td>+0.302$^a$</td>
</tr>
<tr>
<td>PImax (cm H$_2$O) vs TDIcont (mm)</td>
<td>+0.348$^a$</td>
</tr>
<tr>
<td>SPImax (PTU) vs TDI cont (mm)</td>
<td>+0.444$^b$</td>
</tr>
<tr>
<td>FFM (kg/m$^2$) vs TDIcont (mm)</td>
<td>+0.316$^a$</td>
</tr>
<tr>
<td>FMM (kg/m$^2$) vs SPImax (PTU)</td>
<td>+0.254$^b$</td>
</tr>
<tr>
<td>BMI (kg/m$^2$) vs SPImax (PTU)</td>
<td>+0.273$^a$</td>
</tr>
<tr>
<td>FFM (kg) vs SPImax (PTU)</td>
<td>+0.370$^a$</td>
</tr>
<tr>
<td>PAS vs VC (litres)</td>
<td>+0.334$^a$</td>
</tr>
<tr>
<td>PAS vs TLC (litres)</td>
<td>+0.420$^a$</td>
</tr>
<tr>
<td>CRP (μg/ml) vs FMM (kg/m$^2$)</td>
<td>+0.332$^a$</td>
</tr>
</tbody>
</table>

TDIcont=diaphragm thickness at TLC. TR=diaphragm thickening ratio. PImax=maximum inspiratory pressure. SPImax=sustained maximum inspiratory pressure. PTU=pressure time units. FFM=fat-free mass. PAS=physical activity status (in MET's=metabolic equivalents [1 MET=3.5 ml/kg/min]). CRP=C-reactive protein.
related to a reduced VC and TLC \( (p<0.01) \). No other significant correlations for the whole group of patients with CF were identified between variables of TDIrel, FFM, PAS or PImax and SPImax (Table 4).

4. Discussion

The present study has shown that (1) CF patients with severe pulmonary disease and low FFM have poor inspiratory muscle work capacity and function capabilities and reduced diaphragm thickness when compared to CF patients with a normal FFM, (2) CF patients with a normal FFM do not have significantly different inspiratory muscle function, measured as PImax or SPImax, or diaphragm thickness when compared to age-matched healthy subjects, (3) the findings of poor pulmonary function and body composition are consistent with a significant reduction in physical activity, relaxed and contracted diaphragm thickness and thickening ratio in CF patients.

Diaphragm muscle mass is related to an individuals height and weight [27], and loss of as much as 30% of predicted body weight has been found to be associated with a reduction in diaphragm mass, thinning of the muscle, and a reduction in its area [28,29]. This has been shown to be related to sarcomere loss with a reduction in diaphragmatic thickness in malnourished patients with COPD [29] and that in cachetic subjects the reduction in body weight is associated with a decreased contractility of the diaphragm and hence increasing the risk of respiratory failure [30]. Similar studies in severely malnourished CF patients have not been available for comparison as in previous investigations no separation was made for patients with low versus normal FFM [11–13] and the degree of malnutrition has been modest. This lack of separation in terms of disease severity may also account for the high intersubject variability in diaphragm thickness in previous studies as examination of the data in Table 1 demonstrates relatively small variability and no significant difference in diaphragm thickness between patients when compared with the healthy subjects despite small but significant differences in FFM. This is in contrast to the findings when patients were separated into moderate versus severe disease as appreciable differences were demonstrated in both relaxed and contracted diaphragm thickness and which was associated with significant reductions in PImax and single breath work capacity (SPImax).

The preservation of volitional tests of inspiratory muscle strength and diaphragm thickness in patients with CF in previous investigations has been postulated to be the result of a selective ‘training stimulus’ as the load on the inspiratory muscles is increased due to the effects of hyperinflation in patients with chronic lung disease [11–13]. Although the diaphragm has been shown to increase its thickness during training with both respiratory [31,32] and non-respiratory manoeuvres [33,34], this is in contrast to the constant load exerted by lung disease (hyperinflation and increased work of breathing). Skeletal muscle training is applied by the imposition of overload at a specific intensity to obtain a strength or endurance response [35], but requires that this is followed by unloading and planned adaptation. Loads of greater than 60% of peak force are not sustainable [36] and breathing at work levels close to PImax will induce fatigue rather than a required or planned training response unless the breathing strategy is altered to avoid fatigue. Therefore the relative preservation of PImax in patients with hyperinflated lungs may be an adaptive response to loading of the respiratory muscles from the effects of hyperinflation [37] rather than a training response. This is in contrast to the findings in older COPD patients where reductions in PImax are associated with an increase in the proportion of type 1 fibres in the respiratory muscles [38]. This adaptive response allows tolerance of endurance but at the expense of reduced power/ strength capabilities and may reflect a different time course of the disease process or reflect differential response to energy balance between CF and COPD [39].

The finding of decreased work capacity of the inspiratory muscles as measured by SPImax is in agreement with earlier investigations, which demonstrated a reduction in the overall functional capabilities of the inspiratory muscles in malnourished CF patients [26] due to a combination of muscle weakness and lung hyperinflation [40] and loss of diaphragmatic force as contraction approaches TLC [41,42]. Unlike the measurement of PImax, SPImax is a measure of pressure generation over a full range on lung volumes, a manoeuvre which is more closely correlated with inspiratory muscle function in CF patients than PImax [26]. The data in the present study have also identified significant correlations between SPImax and diaphragm thickness but which were not evident with measures of PImax. In addition to this, previous studies of respiratory muscle strength have demonstrated conflicting results which may be due to the small numbers of patients included or to differences in disease severity and hence loss of homogeneity of the study population. This study attempted to control for this by determining body composition, pulmonary function and physical activity status in a large series of patients and comparing these to a group of age-matched healthy subjects. Consequently the design of the study allowed for the identification of differences between groups of CF patients with low versus normal FFM thereby reducing any inherent intersubject variability. When separation for body composition was made these findings support the view that loss of muscle mass is the likely cause of reduced inspiratory muscle function. However other influences which adversely affect the contractile properties of the respiratory muscles include alterations in lung mechanics [40–42], altered oxygen kinetics and a decrease in aerobic capacity of the respiratory muscles [43].

No differences in height, weight and therefore body mass index were found between the CF patients when expressed as a whole group and the healthy subjects although FFM was reduced in the patients and was associated with poor pulmonary function (Table 1). These findings are consistent with previous investigations, which found BMI to be normal in 40% of nutritionally depleted CF patients [44] with many CF
patients with normal BMI showing dissociation in the relationship between BMI and the impairment of lung function. In the healthy subjects FFM was within the limits of a healthy UK population of the same age and sex, although these data were generated from bioelectrical impedance. However, a previous investigation has demonstrated that there was good agreement between measurements taken by DXA and BI for measurements of FFM and LBM [6]. The decline in physical activity in patients with reduced FFM is in agreement with earlier studies and has been shown to result in loss of quadriceps muscle bulk [45].

4.1. Limitations of this study

This study could be criticised for only measuring diaphragm thickness by ultrasonography as previous investigations which have assessed diaphragm bulk in CF have used a combination of methods including twitch transdiaphragmatic pressure and computed tomographic scanning [11,12]. However in the present investigation diaphragm thickness was assessed using a published method [19,20,31] which has demonstrated excellent reproducibility in the measurement of both diaphragm [46] and abdominal muscle thickness [47]. A further limitation of this study is that the helium dilution method was used to measure lung function which is known to underestimate FRC and TLC in patients with airways obstruction who present with poorly or non-ventilated areas in the lung [48] and particularly in those patients with very severe lung disease [49]. As this study compared lung capacities to those of healthy subjects inaccuracies in these measurement may have underestimated the severity of lung disease in the CF patients, particularly those with loss of lean body mass and worsening pulmonary function.

In summary, this study has shown that diaphragm thickness is relatively well preserved in CF adults with normal FFM. However the present study suggests that loss of FFM and worsening pulmonary disease results in loss of inspiratory muscle function and that this is associated with significant atrophy of the diaphragm which is closely related to a reduction in physical activity in CF patients.

Acknowledgment

This study was supported by the Physiotherapy Research Foundation and the Cystic Fibrosis Trust.

Appendix A

Formulae for the calculation of BMI (kg/m²):

\[ \text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2} \]

Formulae for the calculation of the diaphragm thickening ratio:

\[ \text{TR}(\%) = \frac{\text{Diaphragm thickness during MIP manoeuvre at FRC}}{\text{Mean thickness while relaxing at FRC}} \]

Formula for the calculation of reproducibility for diaphragm thickness:

\[ \text{CR}(\%) = \sigma B / (\sigma B + \sigma W) \]

where \( \sigma B \) = between subject variance and \( \sigma W \) = within subject variance.

References


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