Corticosteroids and skeletal muscle function in cystic fibrosis

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Barry, Sinead C., and Charles G. Gallagher. Corticosteroids and skeletal muscle function in cystic fibrosis. J Appl Physiol 95: 1379–1384, 2003. First published June 13, 2003; 10.1152/japplphysiol.00506.2002.—Patients with cystic fibrosis (CF) have reduced peripheral muscle strength. We tested the hypothesis that steroid treatment contributes to muscle weakness in adults with CF. Twenty-three stable CF patients were studied. Measurements included knee extensor (KE), knee flexor (KF), elbow flexor (EF), handgrip (HG), expiratory (PEmax), and inspiratory (Pi max) muscle strengths. Spirometry, body mass index (BMI), and days spent in hospital over the preceding 12 mo (DH) were also measured. Average daily dose of prednisolone over the preceding 12 mo (ADD) was 5.1 mg/day. Pearson’s correlation analysis revealed that ADD correlated significantly with skeletal muscle strengths (KF%, r = −0.63, P < 0.01) with the exception of HG%. These findings are independent of age, BMI, pulmonary function, and DH. Multiple-regression analysis revealed that ADD was the most significant predictor of all measures of skeletal muscle function except HG%. It was independently responsible for 54% of the variance in PEmax%, for 46% of the variance in Pi max%, for 45% of the variance in KE%, for 39% of the variance in KF%, and for 41% of the variance in EF%. Concomitant medications (e.g., theophylline) were shown to have no causative effect. Corticosteroids contribute to the skeletal muscle weakness seen in CF patients. The correlation of proximal muscle strength, but not HG strength, with steroid dosage further supports a cause-effect relationship.

MATERIALS AND METHODS

Twenty-three patients (13 male, 10 female) were recruited from the outpatients department at the National Referral Centre for Adult Cystic Fibrosis at St. Vincent’s University Hospital, Dublin. Diagnosis of CF for each subject was based on clinical features, abnormal sweat test (sweat chloride > 60 mmol/l), and genotyping. All subjects were clinically stable for 1 mo before taking part in the study.

To assess the effects of corticosteroids on skeletal muscle function we measured inspiratory (Pi max), expiratory (PEmax), knee extensor (KE), knee flexor (KF), elbow flexor (EF), and handgrip (HG) strengths. Pulmonary function tests were performed, and total steroid dose over the previous 12 mo was calculated in milligrams per day. All tests were performed during a single visit to the research laboratory. Be-
cause of both ethical and logistical difficulties, it was not possible to include a control group.

The local Ethics Committee approved the study. All patients gave informed consent to the procedures.

**Corticosteroid treatment.** The average daily dose (ADD) of corticosteroids taken during the previous 12 mo was calculated. No subject in the study had taken fluorinated steroids at any time in their past. Corticosteroids included oral prednisolone and intravenous hydrocortisone. Calculation of the ADD involved examination of patient files, patient interviews, and examination of each patient’s local pharmacy notes over the preceding 12 mo. The Irish Health Care system provides free medication to all patients with CF, which is paid retrospectively by the government to each pharmacy. As a result, accurate records are available from the local pharmacy for all medications received by each patient. All doses were converted into prednisolone equivalent and expressed in milligrams per day. We also examined the effects of concomitant therapies (theophylline, antibiotics, etc.) on skeletal muscle function.

**Concurrent medication.** All patients involved in the study continued on their maintenance medication at the time of testing. The following is an account of all medications used by the study population before and during the study: 20 subjects used colomycin nebulized, 1 subject used nebulized tobramycin, 2 subjects used nebulized gentamicin, 18 used pancreatin etc. (1000 mg), 2 subjects used nebulized gentamicin, 1 subject used nebulized tobramycin, 1 subject used cefuroxime orally, 1 subject took co-amoxiclav (500 mg/125 mg), 2 subjects used a combination of colomycin nebulized, 1 subject used nebulized tobramycin, 1 subject used ipratropium bromide and salbutamol in a combination inhaler, 11 subjects used a beclometasone dipropionate inhaler, 1 subject used an ipratropium bromide inhaler, and 6 subjects used a fluistics proximate inhaler.

**Pulmonary function testing.** Forced vital capacity and forced expiratory volume in 1 s (FEV1) were measured by use of a spirometer (Vitalograph Compact 11, Fannin Ireland) according to the recommendations of the American Thoracic Society (32), and predicted normal values (31) were used to calculate the percentage predicted values.

**Respiratory muscle strength.** Mouth pressures during $P_{\text{Emax}}$ and $P_{\text{Emax}}$ at functional residual capacity were measured as indexes of inspiratory and expiratory muscle strength, respectively (25, 36). Pressure was measured with a transducer (P.K. Morgan Pmax), which was calibrated with a manometer before each test. Identical methods to those used by McParland et al. (26) were employed.

**Peripheral muscle strength.** Static contractions were measured by using the Compufet system (Biometrics, Kabelstraat, The Netherlands), which was attached to the rigid arm of the quadriceps bench. Each subject was instructed to push as hard as possible against the rigid arm of the quadriceps bench and to sustain the contraction for 8 s as required by the Compufet software. Visual feedback was given representing contraction time during each voluntary effort. The maximum voluntary contractions were recorded as the best of three contractions for each leg and compared with predicted values (29a). Two practice efforts were performed, and this was followed by sufficient tests until three were achieved within 10% of each other. Bilateral limbs were assessed, and the strength of the stronger limb was used for analysis.

To assess isometric KE, KF, and EF, identical positions to those previously described were employed (29a). An adjustable strap was used to secure the pelvis for both KE and KF and to secure the trunk for EF testing. HG strength was assessed by using the same equipment and methods as previously described (26).

**Data analysis.** Percentage predicted values for isometric peripheral muscle strengths were calculated (29a). Predictive equations for analysis of respiratory muscle strengths are those used by Hamilton et al. (18).

**Statistical analysis.** Data are reported as means ± SD. Correlation among variables was assessed by using Pearson’s correlation coefficient. Stepwise multiple-regression analysis was performed for muscle strengths; variables used in the model included age, gender, body mass index (BMI), FEV1%, FEV2%, and days spent in hospital over the preceding 12 mo. Only variables significantly contributing to the model were retained in the final analysis, and the limits of significance were set at $P < 0.05$.

**RESULTS**

**Patient characteristics.** Patient characteristics are summarized in Table 1. The population was quite diverse with regard to disease state. Nutritional status ranged from significantly malnourished (BMI = 16.4) to normal (BMI = 25.5), whereas airflow obstruction ranged from normal (FEV1 = 108% predicted) to severely obstructed (FEV1 = 25% predicted). Inspiratory muscle strength ranged from 40 to 175% predicted. Expiratory muscle strength also demonstrated a similar spread, with values ranging from 31 to 166% predicted (Table 2). Limb muscle strength also demonstrated a wide variation from significantly weak to normal levels (EF% = 24–105%), but mean strength was reduced for all limb muscles tested.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Means ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>23.3 ± 5.1</td>
<td>18–39</td>
</tr>
<tr>
<td>BMI</td>
<td>20.6 ± 2.5</td>
<td>16.4–25.5</td>
</tr>
<tr>
<td>FEV1%</td>
<td>48.7 ± 24.0</td>
<td>25–108</td>
</tr>
<tr>
<td>FVC%</td>
<td>72.3 ± 20.6</td>
<td>33–112</td>
</tr>
<tr>
<td>DH</td>
<td>31.0 ± 30.9</td>
<td>0–100</td>
</tr>
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</table>

Values are means ± SD for 23 patients (13 men, 10 women). FEV1%, forced expiratory volume in 1 s expressed as percentage predicted; FVC%, forced vital capacity expressed as percentage predicted; DH, days spent in hospital over the previous year; BMI, body mass index.

Table 2. Peripheral muscle strengths expressed as percentage predicted

<table>
<thead>
<tr>
<th></th>
<th>Means ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>KE%</td>
<td>45.7 ± 17.6</td>
<td>15.8–91.3</td>
</tr>
<tr>
<td>KF%</td>
<td>62.0 ± 16.9</td>
<td>31.6–95.5</td>
</tr>
<tr>
<td>EF%</td>
<td>62.6 ± 18.1</td>
<td>24.3–105.0</td>
</tr>
<tr>
<td>HG%</td>
<td>67.9 ± 12.2</td>
<td>48.8–96.7</td>
</tr>
<tr>
<td>$P_{\text{Emax}}$%</td>
<td>94.1 ± 34.2</td>
<td>39.8–175</td>
</tr>
<tr>
<td>$P_{\text{Emax}}$%</td>
<td>102.4 ± 35.8</td>
<td>30.6–166.1</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 23. KE%, percentage predicted knee extensor strength; KF%, percentage predicted knee flexor strength; EF%, percentage predicted elbow flexor strength; HG%, percentage predicted handgrip strength; $P_{\text{Emax}}$%, percentage predicted inspiratory muscle strength; $P_{\text{Emax}}$%, percentage predicted expiratory muscle strength.
Prednisolone ADD was 5.1 mg/day. No subject was treated with corticosteroids for allergic bronchopulmonary aspergillosis.

Relationship between limb muscle and respiratory muscle strengths. Respiratory muscle strength and limb muscle strength correlated significantly with each other \( (P < 0.05) \); \( P_{\text{max}} \) correlated with KE\% \( (r = 0.76) \), KF\% \( (r = 0.64) \), EK\% \( (r = 0.87) \), HG\% \( (r = 0.47) \), and \( P_{\text{Emax}} \% \) (\( r = 0.84 \)). \( P_{\text{Emax}} \% \) was also significantly correlated with limb muscle strength, KE\% \( (r = 0.73) \), KF\% \( (r = 0.62) \), EK\% \( (r = 0.83) \), and HG\% \( (r = 0.51) \).

Relationship between muscle strength and steroid treatment. Using Pearson’s correlation analysis (Table 3; Fig. 1), we assessed the relationship between limb muscle and respiratory muscle strength and steroid dose and found a significant relationship between ADD and KE\%, KF\%, EF\%, \( P_{\text{Imax}} \% \), and \( P_{\text{Emax}} \% \).

Relationship between muscle strength and BMI, FEV1\%, age, and DH. The relationships between muscle forces and BMI, FEV1\%, age, and days spent in hospital (DH) were tested by using Pearson’s correlation analysis (Table 3; Fig. 2). BMI was chosen as a marker of nutritional status in CF. No significant correlations were identified between age and any of the variables of muscle function nor between DH and any of the variables of muscle function. Significant positive correlations were identified between BMI and both \( P_{\text{max}} \% \) and \( P_{\text{Emax}} \% \). Significant positive correlations were also found between FEV1\% and KE\%, \( P_{\text{max}} \% \), and \( P_{\text{Emax}} \% \). Significant negative correlations were identified between ADD and all measures of muscle strength except HG\%. The correlations found between

DISCUSSION

The major new findings of this work are that 1) corticosteroid treatment independently correlates with limb and respiratory muscle strength in patients with CF; 2) the effects of corticosteroid treatment on skeletal muscle function are independent of airflow obstruc-

Table 3. Correlation analysis between muscle forces and BMI, FEV1%, age, and DH

<table>
<thead>
<tr>
<th></th>
<th>KE%</th>
<th>KF%</th>
<th>EF%</th>
<th>HG%</th>
<th>( P_{\text{max}} )%</th>
<th>( P_{\text{Emax}} )%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.29</td>
<td>0.40</td>
<td>0.27</td>
<td>0.30</td>
<td>0.55*</td>
<td>0.54*</td>
</tr>
<tr>
<td>FEV1%</td>
<td>0.56*</td>
<td>0.39</td>
<td>0.40</td>
<td>0.23</td>
<td>0.64*</td>
<td>0.67*</td>
</tr>
<tr>
<td>ADD</td>
<td>-0.67*</td>
<td>-0.63*</td>
<td>-0.64*</td>
<td>-0.26</td>
<td>-0.73*</td>
<td>-0.67*</td>
</tr>
</tbody>
</table>

ADD, average daily dose of corticosteroids over the previous 12 mo. Pearson’s \( r \): *\( P < 0.01 \).

Fig. 1. Correlation of percentage predicted knee extensor strength with average daily dose of corticosteroid over the previous 12 mo.

ADD and KE\% and ADD and respiratory muscle strength (\( P_{\text{max}} \% \) and \( P_{\text{Emax}} \% \)) were more significant than those seen between FEV1\% and KE\% and FEV1\% and respiratory muscle strength.

Determinants of muscle forces using stepwise multiple-regression analysis. Average daily dose predicted 45% of the variance in KE\% with gender being responsible for 24%. (Table 4) Thirty-nine percent of the variance in KF\% was due to ADD. Forty-one percent of the variance in EF\% was related to ADD, with gender being responsible for a further 36%. HG\% had no significant predictors. ADD predicted 54% of the variance in \( P_{\text{Imax}} \% \), with 9% being due to BMI and 13% being due to gender. ADD also explained 46% of the variance in \( P_{\text{Emax}} \% \), with 22% being related to gender. For all muscle groups tested except HG\%, ADD of corticosteroids explained the largest proportion of muscle weakness seen (Table 4). None of the concurrent medications contributed significantly to the regression model. Figure 3 illustrates the lack of correlation between theophylline dose expressed in milligrams per day and KE\%.

Table 4. Stepwise multiple-regression analysis

<table>
<thead>
<tr>
<th></th>
<th>KE%</th>
<th>KF%</th>
<th>EF%</th>
<th>HG%</th>
<th>( P_{\text{max}} )%</th>
<th>( P_{\text{Emax}} )%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<td>NS</td>
<td>NS</td>
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<td>NS</td>
</tr>
<tr>
<td>FEV1%</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>0.24</td>
<td>NS</td>
<td>0.36</td>
<td>NS</td>
<td>0.13</td>
<td>0.22</td>
</tr>
<tr>
<td>BMI</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</tr>
<tr>
<td>DH</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ADD</td>
<td>0.45</td>
<td>0.39</td>
<td>0.41</td>
<td>NS</td>
<td>0.54</td>
<td>0.46</td>
</tr>
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</table>

\( R^2 = \) total variance explained by the significant components of the model; NS, not significant.

Fig. 2. Correlation of percentage predicted knee extensor strength with days spent in hospital over the previous 12 mo.
tion, nutrition, and DH; and 3) this correlation is seen for proximal muscles but not for the distal HG muscles. These results are in support of the hypothesis that treatments with corticosteroids have a negative effect on skeletal muscle strength in CF patients.

Possible limitations of this study are the following: 1) We used an indirect measurement of nutritional status, and no direct measure of lean body mass was performed. However, BMI has been shown to be a valuable measure of nutritional status in CF and to relate to exercise capacity (28), bone mineral density (17), and prognosis (20). 2) Our measures of limb muscle strength and respiratory muscle strength are effort dependent; however, each subject was tested repeatedly by the same investigator, making it difficult to perform repeated submaximal efforts. 3) We did not measure total body muscle mass, and as a result it is difficult to say conclusively whether we are seeing true myopathy, in which strength would be reduced at a disproportionate rate to muscle mass. 4) DH provides a useful marker of periods of extreme disuse; however, activity of daily living may contribute to disuse atrophy and has not been accounted for here.

A number of authors have looked at the presence of limb muscle weakness in CF patients. Lands et al. (24) demonstrated that leg strength was reduced in CF patients compared with controls and that strength was strongly related to body mass ($r = 0.816, P < 0.01$). Mier et al. (27) found that quadriceps strength was on average 68% predicted in their CF group. More recently, de Meer et al. (9) demonstrated that limb muscle force was reduced in CF children even in the absence of reduced pulmonary or nutritional status, whereas Elkin et al. (16) have demonstrated that both limb muscle strength and mass were reduced in their CF group compared with controls. The causes of muscle weakness in CF remain unclear; some authors suggest impairment in the quality of the muscle (9–11, 29), whereas others suggest that the differences in strength seen between CF patients and controls are related to body mass (16, 19, 24). No conclusive data are available at this time.

Studies of respiratory muscle function in CF are difficult to compare because of differences in the age of subjects studied, the methods used, and the indexes of muscle function. The tendency throughout the literature has been for inspiratory strength to be preserved in CF (20, 23, 24, 27, 30), and this is in agreement with our findings. Significant negative correlations were found between $P_{\text{Imax}}\%$, $P_{\text{Emax}}\%$, and ADD (Table 3). Our results demonstrate a wide range of values for $P_{\text{Imax}}\%$ (39.9–175%) with an equally wide range seen for $P_{\text{Emax}}\%$ (30.6–166.1%). We have shown that some patients have preserved respiratory muscle strength, whereas others have markedly reduced strength and still others have supernormal levels of respiratory muscle strength. The mechanisms responsible for these variations in strength are not clear. Factors such as reduced nutritional status, hypoxia, acidosis, electrolyte disturbances, and disuse may contribute to reduced strength, whereas chronic cough and increased work of breathing have been implicated in both preserved and increased respiratory muscle strength. It is likely that a number of factors simultaneously cause respiratory muscle variation. We have demonstrated a relationship between the widely varying respiratory strength seen in adults with CF and ADD, which have not been described previously.

There are many possible factors that can affect skeletal muscle function in CF. Weight loss, protein calorie insufficiency, abnormal ion transport, inflammation, sepsis, electrolyte disturbances, hypoxia, and corticosteroid usage all have myopathic potential. The purpose of this study was to assess the independent effects of corticosteroid therapy on limb muscle strength and respiratory muscle strength in a group of stable CF patients. It is known that myopathy may occur with virtually all steroids in common use (1, 13, 37). There are no previous data, to our knowledge, on the effects of treatment with corticosteroids on muscle strength in CF patients.

Like others, we have demonstrated the presence of limb muscle weakness in adults with CF (9, 16, 24, 27) and the preservation, on average, of respiratory muscle strength (21, 24, 30). We have shown that ADD of corticosteroids is significantly correlated with all measures of skeletal muscle function except HG%. We were unable to identify significant predictors of HG strength. HG was on average reduced at 67.9% predicted. Possible mechanisms of reduced HG strength are similar to those already described for generalized skeletal myopathy, with the exception of corticosteroid usage. These results are in agreement with our biological knowledge of steroid myopathy and its preference for proximal muscle atrophy, hence the lack of correlation with HG%.

Stepwise multiple-regression analysis revealed that ADD was responsible for the largest proportion of the muscle weakness seen in our CF patients, to a greater extent than nutritional status, pulmonary function, and DH. Single-regression analysis revealed a lack of correlation between peripheral muscle forces and $\text{FEV}_{1}\%$, BMI, age, and DH. The only significant corre-
lation found was between KE% and FEV1%; however, this correlation was less than that seen for KE% and ADD. These findings suggest that treatment with corticosteroids contributes to muscle weakness in CF patients.

Nutritional status, disuse, and severity of disease all potentially affect muscle strengths in CF. To control for these potential cofactors, we assessed the effects of FEV1%, BMI, age, gender, and DH on strength of peripheral and respiratory muscles using both single- and multiple-regression analysis. Single-regression analysis revealed a significant relationship between KE% and FEV1%, which was less significant than between KE% and ADD. Stepwise multiple-regression analysis revealed that ADD was the most significant predictor of KE%, KE%, EF%, PImax%, and PEmax% with no significant effect on HG%. These results are in agreement with our hypothesis, i.e., that corticosteroids contribute to skeletal muscle weakness in CF.

In conclusion, this study demonstrates a significant association between corticosteroid dosage and skeletal muscle weakness in adults with CF. This correlation occurs at doses used in clinical practice. The correlation with steroid dosage is much greater than that attributable to age, sex, lung function, or overall nutritional status. These results have significant clinical implications.

DISCLOSURES

We thank the Cystic Fibrosis Research Trust, the Cystic Fibrosis Association of Ireland, the Health Research Board of Ireland, and the National Rehabilitation Board of Ireland for their support. We also thank the Cystic Fibrosis patients at St. Vincent’s University Hospital for their continued support.

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