Effect of acute exacerbations on skeletal muscle strength and physical activity in cystic fibrosis

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Abstract

Background: Skeletal muscle weakness is an important complication of chronic respiratory disease. The effect of acute exacerbations on strength in patients with cystic fibrosis is not known.
Methods: Quadriceps (QMVC) and respiratory muscle strength were measured in patients at the time of acute admission, at discharge and one month later. Patients wore an activity monitor during admission and at one month. Convalescent values were compared to the stable clinic population.
Results: Data were available for 13 acute admissions and 25 stable CF outpatients. Strength and other parameters including daily step count did not differ significantly between the stable and one month post-admission groups. At admission, QMVC was 16.7 (8.3)% lower than at convalescence, whereas inspiratory muscle strength did not change significantly. Reduction in QMVC did not correlate with activity levels or with markers of systemic inflammation.
Conclusion: Further research is needed to identify the mechanisms responsible for the reduction in QMVC.

Keywords: Skeletal muscle; Exacerbation; Physical activity

1. Background

Skeletal muscle impairment is an important complication of chronic respiratory diseases [1–3] and has long been recognised as a feature of cystic fibrosis (CF) [4–10]. The largest study to date, by Troosters et al., identified quadriceps weakness in 56% of adult patients with CF and found it to be associated with functional exercise capacity and time spent in physical activity of moderate intensity [5].

In COPD, acute exacerbations are associated with a reduction in skeletal muscle strength [11,12] and frequent exacerbators experience a more rapid decline in fat free mass [13].

The impact of acute exacerbations on skeletal muscle in CF has not previously been studied. There is some evidence of specific muscle abnormality in CF which may increase the susceptibility of muscle to inflammatory stimuli via NF-κB [14–16]. Exacerbations will increase the level of systemic inflammation and are also likely to be associated with a reduction in daily physical activity with an associated risk of muscle deconditioning.

We therefore measured physical activity and skeletal muscle strength in patients admitted with an acute exacerbation of CF and then repeated the measurements at discharge and one month later once they had convalesced. Values were also compared to a cohort of stable CF patients. The study also allowed us to compare a novel ear worn activity recognition (e-AR) device [17] against the outputs from a commercially available device (The SenseWear Bodymedia Armband).
2. Methods

This was a prospective, observational study which was approved by The Charing Cross Research Ethics Committee (07/H0711/125). All participants provided written informed consent. A convenience sample of adult CF patients admitted over a one month period was enrolled. Patients were eligible to participate if they had been admitted to hospital with an acute exacerbation and excluded if they had other medical conditions significantly reducing their mobility or if they were not expected to be discharged. Measurements made within 48 h of admission were defined as “admission”. Anthropometric data and fat free mass, calculated using bioelectrical impedance analysis (Bodystat Quadscan, Bodystat, Isle Of Man, UK) were recorded. The Quadscan “illness marker” $Z_{200}/Z_5$ (ratio of impedance at 200 Hz and 5 Hz) was also recorded. Test results including albumin, CRP white cell count and haemoglobin as well as microbiology data where available were recorded. Strength measurements were repeated at “discharge” (within 24 h of discharge from hospital) and strength and activity measurements repeated one month later defined as “convalescent”. Patients did not undergo any training program while in the hospital. In addition, a second sample of stable patients attending CF follow up clinics was recruited for comparison with “stable” group (Fig. 1).

2.1. Measures of strength

Maximum isometric quadriceps strength (QMVC) was measured with subjects seated, trying to extend their dominant leg as hard as possible against an inextensible strap connecting their ankle to a strain gauge (Strainstall Ltd, Cowes, UK) [18]. The signal was amplified and passed to a computer running LabView 6 software (National Instruments, Austin, Texas). The force generated was visible to both subject and investigator for positive feedback and repeated efforts were made with vigorous encouragement until there was no improvement in performance. Efforts were sustained for at least 5 s. Subjects rested for about 30 s between each contraction. Handgrip strength in the dominant hand was recorded using a Jamar Handheld dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA) with at least three efforts and a 30 s gap between them. To assess respiratory muscle strength, maximum sniff nasal (SNiP) and static expiratory and inspiratory (PEmax and PImax) mouth pressures were also determined [19,20].

2.2. Physical activity

Subjects wore a multi-sensor accelerometer armband (SenseWear, BodyMedia, Pittsburgh, PA) [5] continuously during their admission and then for a week, starting 3 weeks after discharge. The device is a biaxial accelerometer worn around the patient’s right upper arm with the sensing device located over the subject’s triceps. In addition, galvanic skin response, skin temperature and heat flux are recorded and proprietary algorithms estimate total energy expenditure (TEE), physical activity duration (PAD), average metabolic equivalents (METs), active energy expenditure (AEE), number of steps, duration on body and sleep duration.

![Fig. 1. Study flow chart.](image-url)
Activity data for “admission” are those for the first complete day following admission, and for “discharge” the last complete day in hospital. The stable or convalescent values are averaged over a median of 6 days wear.

While in hospital some of the patients also wore the e-AR activity monitor (Sensixa Ltd). This is a novel, ultra-lightweight (5.6×3.5×1.0 cm, 7.4 g), activity recognition sensor device (e-AR), worn discreetly behind the ear (Fig. 2). The e-AR sensor mainly consists of a tri-axial accelerometer, a microcontroller, a flash memory and a wireless transceiver. Tri-axial accelerometer data are stored and can be downloaded for analysis when the device is placed on a docking station. The ADXL335 accelerometer measures acceleration with a full-scale range of ±3 g. Analogue to Digital Conversion (ADC) of this data results in x, y, and z axes accelerometer channel outputs ranging from 0 to 4095, representing 0–3 V (or −3 g to +3 g). The e-AR device was not worn while patients were sleeping.

An activity index (AI) is calculated from the acceleration signals by averaging the variance per axis, calculated every minute. The e-AR sensor has been used for energy expenditure prediction [21], activity recognition [22] and for post-operative activity monitoring [23].

2.3. Statistical analysis

Analysis was performed using StatView 5.0 (Abacus concepts, Inc., Berkeley, CA, USA). Changes in strength and physical activity over time were assessed using repeated measures ANOVA and post hoc tests. Values were compared between ical activity over time were assessed using repeated measures ANOVA and post hoc tests. Data are expressed as mean (SD) and a p value of <0.05 was taken to be significant.

3. Results

17 patients were recruited for the acute study. One did not comply with activity monitoring while an inpatient so data were available for 16 individuals to cover the inpatient period. Of these, three patients did not return for analysis (1 had gone abroad and two declined further testing). Complete data at one month was therefore available for 13 patients admitted acutely and this was compared to 25 stable patients (Table 1). There was no difference in strength or demographics between the stable clinic patients and those studied one month after an acute exacerbation. In addition, daily step count and other activity parameters did not differ between the two groups, suggesting that they had recovered to a normal activity level.

3.1. Characteristics of combined convalescent and stable clinic population

Combining the 38 patients in the above analysis (convalescent and stable) the only independent correlate of QMVC was weight (r² 0.74 p<0.0001). QMVC was positively associated with other measures of strength; SNIP (r² 0.16 p=0.013); PImax (r² 0.33 p=0.0001); PEmax (r² 0.38 p<0.0001); handgrip (r² 0.57 p<0.0001) and body composition; FFMI (r² 0.44 p<0.0001) as well as with the Z200/Z5 impedance ratio (r² 0.23 p=0.002). Mean step count when stable (n=38) was 7441(4154) steps. Step count did not correlate with anthropometrics, with any measure of strength or with lung function or any blood test parameter.

3.2. Effect of acute exacerbation

In the acute group white cell count 13.6 (3.2)10⁹/L vs. 10.2 (3.3)10⁹/L (p=0.002) and CRP 33.2 (32.3) mg/L vs. 17 (31.5) mg/L (p=0.1) were higher at admission than in the stable group but albumin did not differ 38.5 (4.7) g/l vs 39.1 (4.6) g/l (p=0.8). Mean length of stay was 8.6 (3.6) days. Five patients had documented pseudomonal, 1 cepacia and 2 staphylococcal infections. All were on long term nebulised antibiotics. Three were on long term prednisone and one additional patient

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of stable patients and post-exacerbation patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stable group (n=25)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>33.7 (11.6)</td>
</tr>
<tr>
<td>Gender (%female)</td>
<td>10 (38%)</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>22.1 (1.9)</td>
</tr>
<tr>
<td>FFMI (kg m⁻²)</td>
<td>17.2 (1.8)</td>
</tr>
<tr>
<td>Z200/Z5 impedance ratio</td>
<td>0.73 (0.03)</td>
</tr>
<tr>
<td>QMVC (kg)</td>
<td>38.7 (12.2)</td>
</tr>
<tr>
<td>SNIP (cmH₂O)</td>
<td>88.8 (21.1)</td>
</tr>
<tr>
<td>PImax (cmH₂O)</td>
<td>83.2 (36.9)</td>
</tr>
<tr>
<td>PEmax (cmH₂O)</td>
<td>96.7 (53.7)</td>
</tr>
<tr>
<td>Handgrip (kg)</td>
<td>37.0 (10.3)</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>2.30 (0.96)</td>
</tr>
<tr>
<td>FEV₁ %pred</td>
<td>64.0 (22.9)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>3.69 (1.2)</td>
</tr>
<tr>
<td>FVC %pred</td>
<td>89.8 (21.0)</td>
</tr>
<tr>
<td>Steps (day⁻¹)</td>
<td>7369 (4596)</td>
</tr>
</tbody>
</table>

BMI, body mass index; FFMI, fat free mass index; QMVC, quadriceps maximum voluntary contraction; SNIP, sniff nasal inspiratory pressure; PImax, maximum inspiratory pressure; PEmax, maximum expiratory pressure; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity. Step count measured with SenseWear armband physical activity monitor. p values are for unpaired t tests except gender (Chi²) (*p<0.05).
was treated with a short course of prednisone during their admission. Spirometry improved from admission through discharge to follow up; FEV1 1.54 (0.38)L, 1.64 (0.45)L, 1.81 (0.42) and FEV1%predicted 45.7 (15.4), 51.1 (18.8) and 54.0 (18.2) respectively (both \(p < 0.002\)). Fat free mass increased significantly from admission to convalescence; 47.9 (10.6)kg to 48.7 (10.8)kg (\(p=0.007\)).

3.3. Admission QMVC compared to convalescent values

QMVC rose from admission (Fig. 3, Table 2). Since the values in the convalescent group were not significantly different from those in the stable group we assumed that the convalescent QMVC represented patients’ “normal” strength. On this basis we calculated the percentage reduction in QMVC at the time of admission. Day 1 QMVC was 16.7 (8.3)% lower than in the stable state. The percentage reduction did not correlate significantly with any demographic parameter, length of stay, CRP, albumin or white cell count, treatment with prednisone, activity level or with the percent reduction in step count between day 1 and the stable state. Reduction in strength tended to be negatively associated with albumin (\(r^2 0.18 \ p=0.15\)) and positively with white cell count (\(r^2 0.13 \ p=0.23\)).

3.4. Change in QMVC from admission to discharge

Median (IQR) length of stay was 9.0 (5.8) days. QMVC rose during the course of admission by a mean 8.2 (11.7)% (\(p=0.043\)) and this rise tended to be higher in those with the largest percent reduction in step count (compared to convalescent values) (\(r^2 0.21 \ p=0.11\)) and percent reduction in active energy expenditure (\(r^2 0.18 \ p=0.16\)) and lower average METS on day 1 (\(r^2 0.22 \ p=0.09\)). It was not associated with length of stay or baseline CRP. Increase in QMVC during admission was positively associated with age (\(r^2 0.30 \ p=0.04\)) and BMI (\(r^2 0.22 \ p=0.09\)). Only age was retained in a stepwise model with the above variables with a larger fall in older individuals.

3.5. Comparison of Ear worn activity monitor data

12 patients wore the e-AR device on a mean of 4.8 (2.8) days. Correlations between minute by minute activity index from the-AR device and minute by minute energy expenditure (METS) from the SenseWear armband were calculated. Mean (SD) correlation was 0.6 (0.1) and ranged from 0.42 to 0.74 (all \(p<0.0001\)) (Fig. 4).

4. Discussion

The main finding of the present study was that quadriceps and expiratory muscle strength were significantly reduced at the time of hospital admission in patients with an acute infective exacerbation of cystic fibrosis and that they increased during and after the admission recovering to a normal level, similar to a stable population one month post discharge. In the stable state quadriceps strength was associated with other strength measures and with fat free mass but not

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Discharge</th>
<th>One month post discharge</th>
<th>Repeated measures ANOVA</th>
<th>Admission vs discharge</th>
<th>Discharge vs 1 month</th>
<th>Admission vs 1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>QMVC (kg)</td>
<td>36.2 (8.9)</td>
<td>38.8 (10.6)</td>
<td>43.8 (12.5)</td>
<td>(&lt;0.0001)*</td>
<td>0.043*</td>
<td>0.0009*</td>
<td>0.0003*</td>
</tr>
<tr>
<td>Pmax (cmH2O)</td>
<td>87.1 (22.7)</td>
<td>87.8 (27.7)</td>
<td>94.5 (32.9)</td>
<td>0.20</td>
<td>0.7</td>
<td>0.2</td>
<td>0.15</td>
</tr>
<tr>
<td>PEmax (cmH2O)</td>
<td>83.6 (23.3)</td>
<td>91.5 (45.8)</td>
<td>102.6 (44.0)</td>
<td>(&lt;0.04)*</td>
<td>0.34</td>
<td>0.07</td>
<td>0.03*</td>
</tr>
<tr>
<td>Snip (cmH2O)</td>
<td>89.1 (20.3)</td>
<td>89.4 (24.3)</td>
<td>88.6 (21.3)</td>
<td>0.97</td>
<td>0.77</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>Grip (kg)</td>
<td>33.9 (8.0)</td>
<td>34.6 (8.3)</td>
<td>37.3 (10.2)</td>
<td>(&lt;0.02)*</td>
<td>0.3</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td>Step count (day(^{-1}))</td>
<td>3684 (2805)</td>
<td>5038 (2619)</td>
<td>7507 (3187)</td>
<td>(&lt;0.001)*</td>
<td>0.13</td>
<td>0.008*</td>
<td>0.001*</td>
</tr>
<tr>
<td>Active energy expenditure (kJ day(^{-1}))</td>
<td>1182 (476)</td>
<td>1473 (313)</td>
<td>1725 (529)</td>
<td>(&lt;0.002)*</td>
<td>0.01*</td>
<td>0.06</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

\* means \(p<0.05\)
significantly related to measures of physical activity. In addition, the activity index of the e-AR device worn during the admission correlated well with the energy expenditure data from the SenseWear armband.

4.1. Significance of findings

To our knowledge this is the first study to look at the effects of acute exacerbations on muscle strength in cystic fibrosis. The reduction in quadriceps strength associated with acute exacerbation was of a similar order of magnitude to that seen in acute exacerbations of COPD [11]. Exacerbations were also associated with a reduction in daily physical activity, with a step count at baseline roughly half of that measured in the one month convalescent state with concomitant changes in average and active energy expenditure.

Although some studies have found normal strength and physical performance in children with CF [24] others have found strength to be reduced and associated with a reduction in exercise capacity independent of lung function [25]. The largest study to date (n = 64) by Troosters et al. found weakness in 56% of patients with an association between the quadriceps strength and functional exercise capacity but, as in the present study, not with daily step count [5]. The absence of a relationship between physical activity measures and quadriceps strength in our cohort may be a feature of sample size.

Specific muscle abnormalities have been identified in CF. These may increase the susceptibility of muscle to inflammatory stimuli via NF-κB activation of pro-inflammatory cytokines and the E3 ubiquitin ligases (MuRF1 and atorgin-1) which promote muscle catabolism [14–16]. Interestingly, the systemic inflammatory response to exercise is exaggerated in patients with CF with a greater increase in IL6 and TNFα [26]. In the present study CRP and white cell counts were higher in the exacerbation group, but values did not correlate significantly with change in strength or with strength in the stable state, consistent with one previous study [27]. Muscle endurance as well as strength may be an issue; one study showed that quadriceps fatigue occurred after exercise to a similar extent as in matched controls though strength and exercise capacity were both less [28] and oxidative capacity assessed during exercise using spectroscopy has been shown to be reduced in CF [16,29].

The observation that the Z200/Z5 impedance ratio is associated with quadriceps strength is interesting as this parameter is determined without anthropometric data. It is simple to measure and has the potential to be examined as a biomarker in future studies.

QMVC rose during hospital admission in contrast to what has been observed in acute exacerbations of COPD [11]. However, the patients in the present study did not undergo a training program but were ambulant and activity levels increased through the admission whereas COPD inpatients tend to be very immobile. Moreover, duration of stay was partly determined by the need for intravenous antibiotics rather than the point at which they had recovered sufficiently to cope at home as is the case in COPD.

4.2. Respiratory muscle strength

Studies in CF using volitional techniques and mouth pressures to assess respiratory muscle strength have found it to be relatively well preserved, [5,30–34] except in the context of significant nutritional depletion and hyperinflation [35–37]. In the present study maximum expiratory but not inspiratory pressures were reduced relative to the stable state during acute exacerbation. Abdominal muscle recruitment occurs at lower expiratory threshold loads in CF and in COPD where there is also expiratory flow limitation [38] so the possibility that abdominal muscle fatigue occurs during acute exacerbations needs to be considered [39].

Corticosteroids have been proposed as a cause of skeletal muscle weakness in chronic respiratory disease, though the data to support this possibility in COPD is limited; a two week course of prednisone had no impact on skeletal muscle function [40] and no association has been found between average daily dose of corticosteroids and quadriceps strength in a cross sectional study [41]. However a correlation between corticosteroid exposure and strength has been observed in CF [6] and corticosteroid administration during acute exacerbations may therefore contribute to acute reductions in strength. In the present study no effect of prednisone was
seen but the numbers involved are too small to draw any conclusion from this.

The activity index derived from the e-AR monitor was significantly correlated with data from the Sensewear armband which supports the validity of the former measure. It should be noted that the Sensewear armband, though widely used, cannot be considered a gold standard for measurement of energy expenditure. The algorithms employed have not been validated in this population or context. We did not seek to compare the AI from the e-AR sensor with the raw activity data available from the armband as our purpose was to correlate the e-AR against the processed outputs of the Sensewear armband as the latter are used in practice.

4.3. Critique of the methods

Our findings would have been stronger if we had been able to follow a cohort of patients prior to admission so that we could have directly measured the fall in strength rather than inferring it from the degree of increase in strength back to the convalescent state. However the fact that the patient group at one month post-exacerbation was indistinguishable from the “stable” patients suggests that this may be a reasonable assumption and this model has been used in acute exacerbations of COPD previously [11].

Our study was not able to identify the cause of weakness observed during acute exacerbation. Although it was not significantly correlated with severity factors (CRP, white cell count, and length of stay) or with the degree of reduction in physical activity compared to the stable state the trend to a greater fall in those with the highest white cell count and lowest albumin suggests that exacerbation related factors may be relevant and deserve further consideration. The greater reduction in strength in older individuals is also of interest. Larger studies are needed to clarify this further and our pilot data should help to power these. The severity of exacerbations was such that patients were all able to mobilise, although physical activity levels were reduced, so caution is needed for extrapolating these data to patients with more severe exacerbations.

We used volitional measures of strength raising the possibility that changes seen over time were due to changes in patient motivation. All patients received vigorous encouragement and efforts were repeated until researchers were confident that a maximal effort was being made. The fact that inspiratory efforts were repeated until researchers were confident that a maximal effort was being made. The fact that inspiratory and expiratory muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis. Eur Respir J 2009;33:99–106.


References


