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Respiratory muscle strength in stable adolescent and adult patients with cystic fibrosis

M.A. Dunnink [a], W.R. Doeleman [a], J.C.A. Trappenburg [b], W.R. de Vries [c,*]

[a] *Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands*
[b] *Julius Centre, University Medical Centre Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands*
[c] *Rudolf Magnus Institute of Neuroscience, Section Rehabilitation and Sports Medicine, University Medical Centre Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands*

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Abstract

Background: Since available studies have provided conflicting results, this study investigated respiratory muscle function and its relationship with exercise capacity, degree of dyspnoea and leg discomfort, and quality of life in patients with Cystic Fibrosis (CF).
Methods: Using a cross-sectional design, 27 clinically stable adolescent and adult patients (f/m: 14/13, age: 26 ± 7 years) were included. Data of respiratory muscle strength ($P_i$max and $P_e$max), lung function (spirometry), peripheral muscle strength (peak isometric quadriceps and hand-grip strength), symptom-limited exercise capacity (modified shuttle test, MST), post-exercise dyspnoea and leg discomfort (Borg scores), and quality of life (CFQ-14+, MRC) were obtained for further analysis.
Results: $P_i$max of the total patient group was significantly higher than reference values ($P_i$max = 124 ± 32% predicted), and correlated positively with the walk/run distance of the MST (r_s = 0.59, p = 0.00). Female patients showed more dyspnoea and a more impaired lung function than male patients. However, $P_i$max and $P_e$max (% predicted) showed a tendency to be higher in female than in male patients.
Conclusion: Increased work of breathing will have a conditioning effect on the respiratory muscles, suggesting that training-related inspiratory muscle strength can play a positive role in the limited exercise capacity of CF patients.

Keywords: Exercise capacity; Mouth pressure; Dynamometry; CFQ-14+; Dyspnoea scale

1. Introduction

Available studies of respiratory muscle strength in patients with Cystic Fibrosis (CF) have provided conflicting results, showing either decreased, normal or supernormal values of respiratory muscle strength [1–4]. Hyperinflation and malnutrition seem to be the main factors leading to respiratory muscle weakness [5]. In contrast, chronic cough and increased work of breathing probably leads to functional compensation with a preserved or increased respiratory muscle strength [1]. It is difficult to interpret these studies because of different characteristics of the patients included, such as age, nutritional status and the degree of respiratory dysfunction. In addition different methods and types of measuring respiratory muscle strength were used [1–4].

It has been suggested that reduced respiratory muscle strength in CF patients can play a role in respiratory muscle fatigue and thereby contributing to dyspnoea and ventilatory failure [5]. Respiratory muscle fatigue may be a consequence of an imbalance between workload on, and work capacity of the respiratory muscles. The workload will be increased as a result of airflow obstructions due to inflammatory processes which lead to a high airway resistance. [5] Compared to healthy conditions the work capacity of the respiratory muscles is reduced because of a diminished power and efficiency of the respiratory muscles as a result of malnutrition and/or hyperinflation[6]. In addition, no direct relationship was found between

* Corresponding author. Tel.: +31 887553396; fax: +31 887555450.
E-mail address: w.r.devries@umcutrecht.nl (W.R. de Vries).

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respiratory muscle weakness and the development of hypoxemia and hypercapnia during sleep and/or exercise in CF [7]. In contrast, it is well known that in COPD patients muscle weakness leads to hypercapnia and oxygen desaturation in blood during sleep, as well as socio-economical effects, such as increased medical consumption and decreased survival [8].

Currently a large variation of opinions exists on respiratory muscle strength in CF patients, and there is insufficient knowledge on the symptoms and consequences of respiratory muscle dysfunction in these patients. Therefore, this study investigated the respiratory muscle strength in a group of stable adolescent and adult CF patients. The aim of this study was to assess respiratory muscle function and provide more clearness about the consequences of possible respiratory muscle dysfunction in a representative sample of patients. The following questions were a guideline during the study:

- Is dysfunction of the respiratory muscles present in a group of stable adolescent and adult patients with CF?
- Are there gender-related differences in terms of respiratory muscle strength?
- Is respiratory muscle strength related to exercise capacity, the degree of post-exercise dyspnoea and leg discomfort, and/or quality of life in patients with CF?

2. Subjects and methods

2.1. Patients

The study population consisted of 27 clinically stable adolescent and adult CF patients (f/m: 14/13, age: 26 ± 7 yr (mean ± SD)), recruited from the annual medical check-up for CF patients in the Cystic Fibrosis Centre Utrecht. All patients received a standard medical treatment, consisting of antibiotic- and spray therapy, pancreatic enzymes- and vitamin supplements. No patient used corticosteroids. CF patients who underwent lung transplantation were excluded from this study. All patients gave informed consent to the study, which was approved by the hospital ethical committee. Some anthropometric and lung function characteristics are shown in Table 1 (see Results).

2.2. Study design

A cross-sectional design was used to obtain relevant data during a study period of 3 months. To assess the functional capacity of the patients a number of variables were measured (see below).

2.3. Measurements

2.3.1. Body mass index

The body mass index (BMI) was used to assess weight relative to height and was calculated by dividing body weight (in kg) by height (in m) squared.

2.3.2. Respiratory muscle strength

Respiratory muscle strength was assessed by measuring maximal static expiratory mouth pressure ($P_e$max) starting from total lung capacity (TLC) and maximal static inspiratory mouth pressure ($P_i$max) starting from residual volume (RV). $P_e$max and $P_i$max were determined using a Micro Mouth Pressure Meter (Micro Medical, Rochester, UK). A conventional mouthpiece and nose clip were used. Values were expressed in cmH_2O. Patients had to exhale, respectively, to inspire as forcefully as possible, and with encouragement of the physical therapist the manoeuvre was repeated about 4–8 times. The highest value maintained for 1 s was taken for further analysis. Reference values of Wilson et al. [9] were used for comparison.

2.3.3. Lung function

Forced Expiration Volume in 1 s (FEV_1), Forced Vital Capacity (FVC), their ratio (FEV_1/FVC) and Inspiratory Vital Capacity (IVC) were determined by spirometry (ZAN, Oberthulba, Germany), or with a Microloop (Micro Medical, Rochester, UK). Both devices were calibrated regularly. All variables were expressed as a percentage of the predicted value for healthy subjects, matched for age, body weight, height and gender [10].

2.3.4. Peripheral muscle strength

Measures of peripheral muscle strength included isometric quadriceps and hand-grip strength. The maximal isometric

Table 1
Anthropometric and lung function characteristics of the included CF patients

	Total group (N=27)		Males (N=13)		Females (N=14)		Difference between males and females
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	p-value [a]
Age, year	26 ± 7	18–40	27 ± 8	19–40	25 ± 5	18–34	NS
Height, cm	170 ± 9	151–187	177 ± 6	165–187	163 ± 7	151–176	<0.05
Weight, kg	61 ± 11	36–88	65 ± 9	50–77	57 ± 11	36–88	<0.05
BMI, kg/m^2	21 ± 3	16–29	21 ± 3	18–26	21 ± 3	16–29	NS
FEV_1, l	2 ± 1	1–5	3 ± 1	1–5	2 ± 1	1–4	<0.05
FEV_1, % predicted	63 ± 25	20–105	71 ± 28	29–102	55 ± 22	20–105	NS
FEV_1/FVC, %	65 ± 13	46–89	66 ± 14	46–83	64 ± 12	49–89	NS
IVC, l	4 ± 1	1–6	5 ± 1	2–6	3 ± 1	1–4	<0.05
IVC, % predicted	71 ± 24	29–105	80 ± 20	40–102	62 ± 25	29–105	NS

BMI: Body mass index; FEV_1: Forced Expiration Volume in 1 s; FVC: Forced Vital Capacity; IVC: Inspiratory Vital Capacity; NS: not significant.
[a] t-test for unpaired samples.

quadriceps strength of the dominant leg was assessed with a Cybex dynamometer (Lumex, Ronkonkoma, NY). The subject was positioned with a hip angle of 90° and a knee joint angle of 60°, and stabilized with a trap around the waist, the upper leg and the distal tibia. The best of three repetitions was referred to as peak force development [11]. Maximal hand-grip strength was assessed with a Jamar (TEC, Clifton, NJ) that enabled standardized hand and grip position [12]. Both hands were tested two times, and the peak value for each hand was used for further analysis. Peak values were expressed as a percentage of predicted values for healthy, age and gender matched subjects [11,12].

2.3.5. Exercise capacity

The modified shuttle test (a field test with proven reliability, repeatability and sensitivity in adult CF patients [13]) was used to evaluate the symptom-limited exercise capacity in CF patients. The test is a 15-level, externally paced test that required patients to walk/run at increasing speeds back and forth on a 10 m course. The test starts with a speed of 1.8 km/h (level 1), followed by an increment of 0.6 km/h at each successive level [13]. The test ends when patients become unable to maintain the required speed, fail to complete a shuttle in the time allowed, or attain the maximal distance of 1500 m. During the test heart rate (Polar Electro OY, Finland) and oxygen saturation at the fingertip (Oximetry sensor, Dolphin Medical Inc, Hawthorne, CA) were measured. The tests were supervised by physical therapists, with a physician immediately available in the vicinity of the testing area. For further analysis the total walk/run distance and oxygen saturation were used.

2.3.6. Feelings of post-exercise dyspnoea and leg discomfort

Immediately after the MST, patients were asked to rate subjective feelings of dyspnoea and leg discomfort on an 11-point Borg scale in response to the questions, “how breathless do you feel?”, and, “how much leg discomfort do you feel?”, respectively (score 0 = no symptoms; score 10 = maximal symptoms) [14].

2.3.7. Quality of life

The disease-specific Cystic Fibrosis Questionnaire for adolescents and adults (CFQ-14+) was used to assess the quality of life (QOL) [15]. This questionnaire consists of 47 items, divided into 9 domains. The domains are physical functioning, energy/well-being, emotions, social limitations, role limitations, self-image, eating disturbances, treatment burden, and embarrassment. The symptom scales concern respiratory, digestive and body weight problems. The scores are calculated by a standardized method, with higher scores corresponding to higher QOL [15]. In addition, the Dutch version of the Medical Research Council (MRC) dyspnoea scale was used as a simple and valid method for categorizing patients in terms of their disability due to lung diseases [16]. Patients answered 6 questions about dyspnoea in daily activities. Score 0 indicates “I never experience breathlessness in daily life”, and score 5, “I am too breathless to leave the house”.

2.4. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 12.0, SPSS Inc, Chicago, IL). The *t*-test for unpaired samples was used to compare the data of the male and female CF patients with reference values when data were normally distributed. For data with a skewed distribution log transformation was used. For data which remained non-normally distributed after log transformation, the two sample Kolmogorov–Smirnov test was used. Correlations among variables were calculated by Spearman’s rank correlation coefficient (r_s). Statistical significance was accepted at $p \leq 0.05$, and results are presented as means ± SD, unless otherwise stated.

3. Results

Anthropometric and lung function characteristics of the patients are presented in Table 1. Male patients were higher and heavier than females, and showed higher values of FEV_1 and IVC.

Table 2 shows the results of the respiratory muscle strength and the comparison with the predicted reference values expressed in %. $P_i$max of the total group was significantly higher than reference values ($p = 0.00$), whereas $P_e$max was not different from these values ($p = 0.24$). $P_i$max and $P_e$max in female patients were significantly lower than in male patients. However, expressed as a percentage of the predicted values, these values were higher in female than in male patients, although this difference was not statistically significant.

The results of peripheral muscle strength, exercise capacity, oxygen saturation, feelings of post-exercise dyspnoea and leg

Table 2
Respiratory muscle strength of the included CF patients

	Total group ($N=27$)		Males ($N=13$)		Females ($N=14$)		Difference between males and females
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	*p*-value
$P_i$max, cmH_20	113 ± 30	58–160	131 ± 22	86–160	96 ± 26	58–156	<0.05 [a]
$P_e$max, cmH_20	129 ± 43	61–246	153 ± 42	100–246	107 ± 30	61–173	<0.05 [a]
$P_i$max, % predicted	124 ± 32	82–226	115 ± 19	82–152	133 ± 39	90–226	NS
$P_e$max, % predicted	107 ± 32	66–172	100 ± 31	68–171	114 ± 32	66–172	NS

$P_i$max: maximal inspiratory pressure; $P_e$max: maximal expiratory pressure; NS: not significant.
[a] *t*-test for unpaired samples.

Table 3
Peripheral muscle strength, exercise capacity, oxygen saturation, post-exercise feelings of dyspnoea and leg discomfort, and MRC dyspnoea scale of the included CF patients

	Total group (N=27)		Males (N=13)		Females (N=14)		Difference between males and females
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	p-value
HG left, kg	36 ± 15	8–62	48 ± 11	28–62	26 ± 9	8–42	<0.05 [a]
HG right, kg	39 ± 16	13–75	51 ± 11	30–75	27 ± 8	13–40	<0.05 [a]
HG left, % predicted	92 ± 28	28–145	97 ± 22	51–127	87 ± 34	28–145	NS
HG right, % predicted	88 ± 22	45–136	94 ± 21	61–136	82 ± 21	45–118	NS
QF, N	179 ± 72	73–368	227 ± 72	83–368	134 ± 33	73–190	<0.05 [a]
QF, % predicted	60 ± 24	22–131	72 ± 27	22–131	48 ± 11	30–75	<0.05 [b]
MST, m	1040 ± 382	450–1500	1314 ± 307	450–1500	786 ± 247	460–1070	<0.05 [b]
SaO2, %	86 ± 7	64–94	82 ± 10	64–93	89 ± 4	81–94	NS
HR, bpm	174 ± 14	140–196	178 ± 17	140–193	171 ± 12	158–196	NS
Post-exercise dyspnoea feelings	7 ± 2	4–10	6 ± 2	4–8	7 ± 2	5–10	NS
Post-exercise leg discomfort	6 ± 2	2–10	6 ± 2	3–9	6 ± 2	5–10	NS
MRC dyspnoea scale	2 ± 1	0–4	2 ± 1	0–3	3 ± 1	2–4	<0.05 [b]

QF: quadriceps force; MST: modified shuttle test; SaO2: oxygen saturation at the end of the MST; HR, bpm: heart rate in beats per minute at the end of the MST; MRC: medical research council; NS: not significant.
[a] t-test for unpaired samples.
[b] Kolmogorov–Smirnov test.

discomfort, and dyspnoea in daily activities are presented in Table 3. Peripheral muscle strength, expressed in absolute values was significantly lower in female than in male patients. As percentage of predicted values quadriceps force was significantly lower in female patients than in male patients. Also the walk/run distance of the MST was less in females than in males. In addition, the MRC score showed that female patients experienced more dyspnoea in daily life than male patients.

Table 4 shows the CFQ scores of the CF patients. The female patients showed only significantly lower scores than male patients for physical functioning and respiratory problems.

The relationship between respiratory muscle strength and other variables showed for the total group a positive correlation between $P_i$max and the total walk/run distance of the MST (r_s=0.59, p=0.001). $P_i$max was also significantly correlated with social limitations of the CFQ-14+ (r_s=0.63, p=0.001). $P_i$max and $P_e$max were positively correlated with the peak hand-grip and quadriceps forces. The correlations between $P_i$max and peak hand-grip force left and right were r_s=0.50 (p=0.008), and r_s=0.60 (p=0.001), respectively, and with peak quadriceps force r_s=0.56 (p=0.003). For $P_e$max the following correlations were calculated: with peak hand-grip force left: r_s=0.60 (p=0.001), with peak hand-grip force right: r_s=0.60 (p=0.001), and with peak quadriceps force: r_s=0.53 (p=0.005). No correlations were found between respiratory muscle strength and the MRC scale scores or the category scores for dyspnoea.

The male patients showed significant correlations between $P_i$max and lung function (with FEV_1% pred: r_s=0.66, (p=0.014), with FEV_1/FVC: r_s=0.65, (p=0.016), and with IVC% pred.: r_s=0.71, (p=0.007)). $P_i$max was also correlated with different domains and symptom scales of the CFQ (social

Table 4
Scores of the Cystic Fibrosis Questionnaire (CFQ-14+) for the included CF patients

Domains and symptom scales	Total group (N=27)		Males (N=13)		Females (N=14)		Difference between males and females
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	p-value
Physical functioning	74 ± 22	17–100	82 ± 23	17–100	67 ± 20	29–92	<0.05 [b]
Role limitations	80 ± 18	42–100	84 ± 18	50–100	77 ± 18	42–100	NS
Energy/well-being	62 ± 17	17–92	69 ± 16	42–92	56 ± 17	17–79	NS
Emotions	75 ± 24	17–92	82 ± 17	40–100	69 ± 28	0–100	NS
Social limitations	75 ± 15	39–94	81 ± 16	39–94	71 ± 12	56–89	NS
Self-image	87 ± 19	33–100	85 ± 19	33–100	88 ± 19	44–100	NS
Eating disturbances	89 ± 16	44–100	93 ± 15	56–100	85 ± 16	44–100	NS
Treatment burden	72 ± 22	22–100	76 ± 23	22–100	69 ± 21	33–100	NS
Embarrassment	58 ± 21	11–89	63 ± 22	11–89	53 ± 19	11–79	NS
Body weight problems	80 ± 27	0–100	81 ± 30	0–100	80 ± 25	33–100	
Respiratory problems	72 ± 14	50–100	79 ± 13	56–100	67 ± 13	50–89	<0.05 [a]
Digestive problems	83 ± 16	33–100	84 ± 10	67–100	81 ± 21	33–100	NS

NS: not significant.
[a] t-test for unpaired samples.
[b] Kolmogorov–Smirnov test.

limitations, self-image, treatment burden, respiratory problems ($r_s \geq 0.61$, $p \leq 0.05$)), and with the MRC dyspnoea scale ($r_s = 0.63$, $p \leq 0.05$). In female patients the $P_i$max showed only statistically significant correlations with the Borg scores of dyspnoea and leg discomfort ($r_s = 0.58$, and 0.62, $p \leq 0.05$, respectively). In contrast to the correlations calculated for the total group, the male as well as the female patients showed no correlations between respiratory and peripheral muscle strength.

4. Discussion

We evaluated respiratory muscle strength in stable adolescent and adult CF patients. The CF patients in the present study showed a significantly higher $P_i$max compared to reference values, whereas $P_e$max remained within the range of these values. This suggests that an increased work of breathing as a consequence of airway obstruction may have a conditioning effect on respiratory muscles in CF patients. This result is in line with the results of several other studies [1,4,17] that also showed that severe respiratory muscle weakness was uncommon in CF. No significantly increased respiratory muscle strength was found in these studies, in spite of the comparable degree of airway obstruction with the patients in the present study [1,4]. Barry and Gallagher [1] found a negative relationship between corticosteroid medication and respiratory muscle strength. They concluded that corticosteroids have a negative effect on respiratory muscle strength. In the present study, no patients used corticosteroids during the time period that they were tested, and this can be the reason that we observed an increase in inspiratory muscle strength. In contrast, we observed a decreased peripheral muscle strength in our patient group (QF = 60%, HG left = 92%, and HG right = 88% of the predicted reference values). Previous studies with CF patients [1,4] showed also decreased peripheral muscle strength. The patients in the study of Mier et al. [4] had a mean QF of 68%, and the patients in the study of Barry and Gallagher [1] had a mean QF of about 46% and a HG of about 68% of the predicted reference value. Therefore, in contrast to an increased respiratory muscle strength in our group of CF patients, we observed a decreased peripheral muscle strength, probably due to physical inactivity, an intrinsic muscle defect, malnutrition or a combination of these factors [3,18].

The results of the present study are in contrast to the studies of Lands et al. [3] and Szeinsberg et al. [19], who found a reduced $P_i$max and $P_e$max, despite the fact that the lung function of their patients was comparable to the data of the present study. Both studies [3,19] showed that malnutrition can result in decreased respiratory muscle strength. The mean BMI values of the CF patients in these studies (17.58 and 20.57 kg/m^2, respectively) were slightly lower than in the present study (21.2 kg/m^2), indicating that malnutrition was more important in their study population than in our patients. Lands et al. [3] and Szeinberg et al. [19] also found that the degree of hyperinflation was an important determinant of a decreased inspiratory muscle strength. Although the degree of hyperinflation was not measured in the present study, our results indicate that hyperinflation in our patients was not a limiting factor.

This study focused also on gender-related differences in respiratory muscle strength. No statistically significant differences between male and female patients were found when $P_i$max and $P_e$max were expressed as % of predicted values, although these values were higher in female patients. Concerning the lung function, the male patients had a significantly better FEV_1 and IVC, and as % of predicted, these lung functions are clearly higher than in the female patients. In addition, the peak quadriceps force (in absolute values and expressed as % pred.), the peak hand-grip force (in absolute values), the MRC dyspnoea scores, the CFQ domain physical functioning, and the CFQ symptom respiratory problems were significantly higher in male patients than in female patients. Therefore, female CF patients were in a more severe state of the disease, due to a decreased lung function and lower MRC- and CFQ scores. We suggest that as compensation the respiratory muscle strength will be relatively higher in the group of female CF patients. This is in agreement with observations in previous studies in CF patients [4,17], in which no respiratory muscle weakness was found.

Another focus was the relationship between respiratory muscle strength and exercise capacity, degree of dyspnoea and leg discomfort, and quality of life. A positive correlation was found between inspiratory muscle strength and the walk/run distance of the MST. This suggests that a training-related inspiratory muscle strength can play a positive role in the limited exercise capacity of CF patients. It is conceivable that a better inspiratory muscle strength will compensate the negative effects of a reduced lung function on the walk/run performance. A positive correlation was also found between $P_i$max and the Borg scores of leg discomfort. This is in line with a study of Enright et al. [20], who showed a positive effect on exercise capacity after a high-intensive training of respiratory muscles. In contrast to our expectations, we could not calculate a significant correlation between $P_i$max and Sa_{O2}% during exercise. Moreover, there was no significant gender-related difference in Sa_{O2}% during exercise (see Table 3). We are not able to compare these results with those of other studies, because studies that are focused on these correlations in CF patients are lacking. The present study found no significant correlations between respiratory muscle strength and the MRC dyspnoea scale or the Borg scores of dyspnoea. This is consistent with results of a study of De Jong et al. [6], who found no changes in the degree of dyspnoea in CF patients after respiratory muscle training. Our study showed also a positive correlation between $P_i$max and social limitations, indicating that a higher $P_i$max was associated with a lower score on social limitations. This observation is in contrast to the results of a previous study with CF patients [20], probably due to the use of different questionnaires on QOL. Our study used a questionnaire specifically developed for CF patients, while Enright et al. [20] used a questionnaire that was validated for patients with chronic obstructive lung diseases.

Before drawing conclusions from this study, some limitations must be acknowledged. A potential limitation could be the

fact that a small number of clinically stable patients were included. Thus, our findings cannot be generalized to CF patients, who are not clinically stable. Another limitation may be that the small study population was characterized by a heterogeneity of physical characteristics. For future studies we recommend to include patients based on their degree of airway obstructions, because this study suggests that the presence of airway obstruction may have a conditioning effect on respiratory muscles. Such a study design may contribute to more knowledge about the relationship between respiratory muscle strength and the severity of airway obstruction.

In conclusion, this study showed an increased $P_i$max in stable adolescent and adult CF patients. Compared to male patients, the more severe CF disease in female patients leads to higher predicted $P_i$max and $P_e$max values, although this difference was not statistically significant. These results suggest that increased work of breathing will have a conditioning effect on respiratory muscles. The positive correlation between respiratory muscle strength and exercise capacity indicates that training-related inspiratory muscle strength can play a positive role in the limited exercise capacity of CF patients.

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