Chronic *Pseudomonas aeruginosa* Infection and Respiratory Muscle Impairment in Cystic Fibrosis

Theodore G Dassios MD, Anna Katelari MD, Stavros Doudounakis MD, and Gabriel Dimitriou MD PhD

BACKGROUND: Chronic infection with *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) is associated with increased morbidity. Chronic infection can cause limb and respiratory muscle compromise. Respiratory muscle function can be assessed via maximal inspiratory pressure (P_{Imax}), maximal expiratory pressure (P_{Emax}), and the pressure-time index of the respiratory muscles (PTI_{mus}). We studied the effect of chronic *P. aeruginosa* infection on respiratory muscle function in patients with CF. METHODS: This cross-sectional study assessed P_{Imax}, P_{Emax}, PTI_{mus}, FEV_1, FVC, maximum expiratory flow during the middle half of the FVC maneuver, body mass index, and upper arm muscle area in 122 subjects with CF, in 4 subgroups matched for age and sex at different stages of *P. aeruginosa* infection, according to the Leeds criteria. We compared respiratory muscle function in the subgroups according to *P. aeruginosa* infection state. RESULTS: Median P_{Imax} was significantly lower in CF subjects with chronic *P. aeruginosa* infection (P_{Imax} = 62 cm H_2O), compared to subjects who were never infected (P_{Imax} = 86 cm H_2O, $P = .02$), free of infection (P_{Imax} = 74 cm H_2O, $P = .01$), or intermittently infected (P_{Imax} = 72 cm H_2O, $P = .02$). Median PTI_{mus} was significantly increased in CF subjects with chronic *P. aeruginosa* infection (PTI_{mus} = .142), compared to subjects who were free of infection (PTI_{mus} = .102, $P = .006$). Median upper-arm muscle area was significantly lower in CF subjects with chronic *P. aeruginosa* infection (upper-arm muscle area = 2,219 mm^2), compared to subjects who were never infected (2,754 mm^2, $P = .03$), free of infection (2,678 mm^2, $P = .01$), or intermittently infected (2,603 mm^2, $P = .04$). Multivariate logistic regression revealed *P. aeruginosa* state of infection as a significant determinant of PTI_{mus} ($P = .03$) independently of sex, upper-arm muscle area, and FEV_1. CONCLUSIONS: CF subjects with chronic *P. aeruginosa* infection exhibited impaired respiratory muscle function and decreased inspiratory muscle strength, and chronic *P. aeruginosa* infection independently impacts respiratory muscle function in subjects with CF. *Key words: cystic fibrosis; respiratory muscles; Pseudomonas aeruginosa*. [Respir Care 2014;59(3):363–370. © 2014 Daedalus Enterprises]

Introduction

Pseudomonas aeruginosa infection in patients with cystic fibrosis (CF) is a major determinant of lung disease, and is associated with severe pulmonary disease[1] and increased morbidity and mortality.[2] *P. aeruginosa* infection is associated with gradually declining pulmonary status in children and young adults with CF, as assessed by lung function studies.[3,4] Furthermore, chronic pulmonary infec-

Drs Dassios and Dimitriou are affiliated with the Department of Paediatrics, University of Patras Medical School, Patras, Greece. Drs Katelari and Doudounakis are affiliated with the Department of Cystic Fibrosis, Aghia Sophia Children's Hospital, Athens, Greece. Dr Dassios is also affiliated with Addenbrooke's Hospital, Cambridge University Hospitals, National Health Service Foundation Trust, Cambridge, United Kingdom.

The authors have disclosed no conflicts of interest.

Correspondence: Theodore G Dassios MD, Addenbrooke's Hospital, Cambridge University Hospitals National Health Service Trust, Hills Road, Cambridge, CB2 0SW, United Kingdom. E-mail: tdassios@upatras.gr.

DOI: 10.4187/respcare.02549

tion with *P. aeruginosa* is associated with deteriorating nutrition state, to the point of malnourishment.[5] Sex differences relating to the natural history of *P. aeruginosa* infection have been described in the literature: women suffer higher rates of colonization and younger age of conversion to the more aggressive mucoid phenotype, compared to men.[6,7] Chronic infection has been linked to compromised diaphragm function in animal models[8] and human patients.[9]

Respiratory failure in CF is caused by parenchyma destruction, recurrent infection, and bronchiectasis, and respiratory muscle dysfunction might also play a critical role. Respiratory muscle compromise in CF can lead to respiratory muscle fatigue and thus contribute to respiratory failure. Respiratory muscle strength can be assessed by measurement of maximal inspiratory pressure (P_{Imax}) and maximal expiratory pressure (P_{Emax}).[10] Respiratory muscle strength has been assessed in numerous studies, and conflicting evidence has been presented on whether it is decreased, maintained, or decreased in patients with CF, as was recently highlighted.[11] While some studies advocate that the chronically increased work load against which the respiratory muscles are forced to operate in CF exerts a conditioning effect,[12] other studies support that chronic malnutrition and hyperinflation impact on respiratory muscle strength.[13,14] Hyperinflation, airway obstruction, and malnutrition have been recognized as the major determinants of respiratory muscle compromise in CF patients.[13-15]

To our knowledge, the effect of chronic *P. aeruginosa* infection on respiratory muscle function has not been previously studied in CF patients. We hypothesized that CF patients chronically infected with *P. aeruginosa* would have impaired respiratory muscle function, compared to CF patients who are not chronically infected. Our aim was to compare respiratory muscle function by measurement of P_{Imax}, P_{Emax}, and the pressure-time index of the respiratory muscles (PTI_{mus}) between CF patients at different stages of *P. aeruginosa* infection in a large cohort of children and young adults.

QUICK LOOK

Current knowledge

Chronic infection with *Pseudomonas aeruginosa* in patients with cystic fibrosis is associated with increased morbidity, including limb and respiratory muscle dysfunction.

What this paper contributes to our knowledge

Cystic fibrosis patients with chronic *P. aeruginosa* infection had impaired respiratory muscle function and decreased inspiratory muscle strength. Chronic *P. aeruginosa* infection independently impacted respiratory muscle function in patients with cystic fibrosis.

Methods

This study was approved by the ethics committee of, and performed at, Aghia Sophia Children's Hospital, Athens, Greece. All subjects, or their parents or legal guardians, gave informed written consent prior to the study.

Subjects

We recruited subjects from patients attending their follow-up appointments in our CF department. CF diagnosis was confirmed by sweat-test and expanded mutation analysis. All the subjects received standard daily chest physical therapy. We excluded patients who were unable to perform reproducible lung function tests; patients who had an exacerbation during the month prior to assessment;[16] patients on steroids, anti-inflammatories, or azithromycin; and patients who had positive respiratory cultures for *Aspergillus* species, *Stenotrophomonas* species, *Scedosporium* species, *Burkholderia* species, methicillin-resistant *Staphylococcus aureus*, or any pathogen other than *S. aureus* and *Haemophilus influenzae* in the 5 years prior.

Sample Size

Power analysis was conducted to determine the sample size required to identify PTI_{mus} differences between 4 subgroups: never had *P. aeruginosa* infection; no *P. aeruginosa* infection at assessment; intermittent *P. aeruginosa* infection; and chronic *P. aeruginosa* infection. The PTI_{mus} standard deviation was set at 0.03.[15] The power analysis indicated that detecting a PTI_{mus} increase of 0.05 at a power of 0.9 and a statistical significance of $P < .05$ would require 8 subjects in each subgroup.

Measurements

Flow was recorded with a pneumotachograph (Mercury F100L, GM Instruments, Kilwinning, Scotland) connected to a differential pressure transducer (DP45, Validyne Engineering, Northridge, California, range $\pm$ 3.5 cm H_2O). Airway pressure was measured from a side port on the pneumotachograph, with a differential pressure transducer (DP45, Validyne Engineering, Northridge, California, range $\pm$ 225 cm H_2O). A carrier amplifier (CD280, Validyne Engineering, Northridge, California) was used to amplify the signals from the differential pressure transducers. The amplified signals were recorded with analog-to-digital sampling at 100 Hz (NI PCI-6036E, National Instruments,

Austin, Texas) and analyzed with data analysis software (Labview, National Instruments, Austin, Texas).

Respiratory Pressures

We measured P_{Imax}, P_{Emax}, airway-occlusion pressure at 0.1 s after the start of inspiration ($P_{0.1}$), breathing frequency, tidal volume, minute ventilation, inspiratory time (T_I), and total breathing cycle time (T_{tot}). $P_{0.1}$ was measured during quiet breathing; at least 5 airway occlusions were performed, and the average $P_{0.1}$ value was calculated. P_{Imax} was measured starting at residual volume, with a maximal inspiratory effort against an occluded airway.[17] P_{Emax} was measured starting at total lung capacity, with a maximal expiratory effort against an occluded airway.[17] Five maximal reproducible respiratory efforts were performed, and the maximum value was recorded.[10] The occlusions were performed with a unidirectional valve connected to the mouthpiece (total dead space 8 mL). Care was taken to eliminate any leak around the mouthpiece; a small leak prevented artificial glottic closure.[10] Only P_{Imax} and P_{Emax} maneuvers with plateau pressure for at least 1 s were accepted for analysis.[10] We also calculated the percent-of-predicted P_{Imax} and P_{Emax} values.[18]

Pressure-Time Index of the Respiratory Muscles

Respiratory muscle function was evaluated as PTI_{mus}, calculated as:

$$PTI_{mus} = (\text{mean } P_I/P_{Imax}) \times (T_I/T_{tot})$$

where P_I is airway pressure during inspiration, calculated as

$$P_I = 5 \times P_{0.1} \times T_I$$

PTI_{mus} is a composite index of respiratory muscle function[15,19] that describes the efficiency of the respiratory muscles and the balance between neuromuscular competence and respiratory load. A higher PTI_{mus} indicates inefficient respiratory muscle function and is related to increased risk of respiratory muscle fatigue.[20]

Lung Function Tests

FEV_1, maximal expiratory flow during the middle half of the FVC maneuver, and FVC were measured (MasterScreen, Erich Jaeger/CareFusion, San Diego, California) per the European Respiratory Society guidelines, and are expressed as percent-of-predicted values.[21,22] The values recorded were those achieved before the use of bronchodilator drugs.

Nutrition Assessment

Height and weight were measured, and the corresponding body mass index (BMI) and BMI Z score were calculated.[23] Midarm muscle circumference was measured halfway between the acromion and the olecranon to the nearest centimeter, right hand hanging relaxed.[24] Triceps skinfold thickness was measured (Harpenden Skinfold Caliper, Baty International, West Sussex, United Kingdom) to the nearest millimeter, halfway over the triceps muscle, skinfold parallel to the upper arm longitudinal axis.[24] Upper-arm muscle area was calculated from the midarm muscle circumference and triceps skinfold thickness.[25]

Classification of *P. aeruginosa* Infection State

The Leeds criteria were used to classify *P. aeruginosa* infection state.[26] The infection was classified as chronic when $> 50\%$ of the months sampled had *P. aeruginosa* positive culture; intermittent when $\leq 50\%$ of the months sampled had *P. aeruginosa* positive culture; free of infection when *P. aeruginosa* culture had been negative over the previous 12months, after having previously been *P. aeruginosa* culture positive; and never infected when *P. aeruginosa* had never been cultured from sputum or cough swab. At least 6 airway cultures were acquired in separate months over the year before the assessment.[26] Sputum was collected in sterile disposable containers, stored at ambient temperature, and processed within 4 h from collection. Sputum samples were inoculated and incubated aerobically at 37°C for 48 hours, then analyzed for *P. aeruginosa* and other pathogens. *P. aeruginosa* positive cultures were identified as either mucoid or non-mucoid phenotype.

All the subjects who were chronically infected with *P. aeruginosa* were regularly treated with inhaled antibiotics.

Protocol

All the subjects were assessed in the same setting, with the same medical instruments. All the subjects were in stable clinical condition and had received their medications as usual. They were evaluated in the morning hours, and the assessments were in the following order: nutrition assessment, pulmonary function testing, respiratory muscle assessment. All the subjects were evaluated in a sitting position, and a nose clip was used in the pulmonary function and respiratory muscle studies.

Statistical Analysis

Data were checked for normality with the Kolmogorov-Smirnoff and Shapiro-Wilk tests. Differences between

groups were assessed for significance with the Kruskal-Wallis rank-sum test and the Pearson chi-square test, as appropriate. If a significant difference was detected, the Mann-Whitney rank-sum test was used for subsequent pairwise comparisons between the subgroups. Multivariate logistic regression was performed to determine which variables contribute to alterations of PTI_{mus}. $P < .05$ was considered a significant difference. Statistical analysis was performed with statistics software (SPSS 17.0, SPSS, Chicago, Illinois).

Results

Subjects

Between October 2009 and June 2010, 122 subjects (68 male) were included in the study. The median age was 13 y (IQR 10–17 y), and 13 subjects were > 19 years old. The median BMI Z score was 0.22 (IQR −0.49 to 0.84). The median percent-of-predicted FEV_1 was 99% (IQR 75–119%).

The 4 subgroups were matched for age and sex: group 1 consisted of 11 subjects that had never been infected by *P. aeruginosa*, group 2 consisted of 33 subjects who were free of *P. aeruginosa* infection at the time of assessment, group 3 consisted of 39 subjects with intermittent *P. aeruginosa* infection, and group 4 consisted of 39 subjects with chronic *P. aeruginosa* infection. As the power analysis showed that 8 subjects in each group were required, the sample size per group was deemed appropriate. In group 4, 17 of 39 subjects (43.6%) were chronically infected with the mucoid *P. aeruginosa* phenotype. Since the data were not normally distributed, non-parametric tests were applied to compare the subgroups.

Anthropometry and Nutrition

There were no significant differences in height or weight between the 4 subgroups (Table 1). There were significant differences in BMI Z score between the 4 subgroups ($P = .02$). Post hoc analysis revealed that the median BMI Z score was significantly lower in group 4 than in group 1 ($P = .009$) or group 3 ($P = .02$). There were significant differences between the 4 groups in midarm muscle circumference ($P = .001$), triceps skinfold thickness ($P = .02$), and upper-arm muscle area ($P = .03$). Post hoc analysis revealed significantly lower midarm muscle circumference in group 4 than in group 1 ($P = .003$), group 2 ($P = .003$), or group 3 ($P = .002$), and significantly lower triceps skinfold thickness in group 4 than in group 2 ($P = .05$) or group 3 ($P = .006$).

Lung Function, Respiratory Muscle Function, and Breathing Cycle Components

There were no significant differences between the 4 subgroups in breathing frequency, tidal volume, tidal volume per kilogram, minute ventilation, inspiratory flow, T_I, T_{tot}, T_I/T_{tot}, $P_{0.1}$, mean P_I, or P_{Emax}. There were significant differences in P_{Imax} (Fig. 1) and percent-of-predicted P_{Imax} ($P = .043$ and .037, respectively), and post hoc analysis revealed significantly lower P_{Imax} in group 4 than in group 1 ($P = .044$), group 2 ($P = .01$), or group 3 ($P = .046$), and significantly lower percent-of-predicted P_{Imax} in group 4 than in group 2 ($P = .009$) or group 3 ($P = .02$). Non-parametric testing revealed significant differences in mean P_I/P_{Imax} and PTI_{mus} ($P = .02$ and $P = .03$, respectively). The mean P_I/P_{Imax} was significantly lower in group 4 than in group 2 ($P = .005$), and PTI_{mus} (Fig. 2) was significantly higher in group 4 than in group 2 ($P = .006$). In group 4 the subjects who had mucoid *P. aeruginosa* had a median P_{Imax} of 59 cm H_2O, whereas the group-4 subjects who had non-mucoid *P. aeruginosa* had a median P_{Imax} of 66 cm H_2O ($P = .15$).

Multivariate logistic regression analysis revealed that *P. aeruginosa* infection state was significantly related to PTI_{mus}, independently of FEV_1, upper-arm muscle area, and sex (Table 2).

Discussion

Our study found that PTI_{mus} was significantly increased and P_{Imax} was significantly decreased in CF subjects with chronic *P. aeruginosa* infection, compared to those who were free, never infected, or intermittently infected. The chronically infected patients also had compromised somatic muscular indices, such as midarm muscle circumference and upper-arm muscle area.

Our results suggest that chronic *P. aeruginosa* infection impacts respiratory muscle function in the context of normal lung-function parameters, probably identifying chronic *P. aeruginosa* infection as an independent determinant of respiratory muscle compromise in CF. Our findings emphasize the multifactorial origin of respiratory muscle impairment in the pathophysiology of respiratory failure in CF.

Chronic pulmonary infection with *P. aeruginosa* affects the majority of CF subjects by adulthood,[27] and increases mortality and morbidity in CF patients,[2] and harms pulmonary status in children with CF.[3] *P. aeruginosa* plays a central role in the vicious cycle of pulmonary infection, pulmonary inflammation, lung tissue damage, and consequent respiratory failure.[28]

Although systemic inflammation is not a major component of CF disease, pulmonary inflammation has been suspected to cause limb and respiratory muscle wasting and

Table 1. Anthropometric, Pulmonary, and Respiratory Muscle Function Data According to Different Stages of *Pseudomonas aeruginosa* Infection

	Group 1 (n = 11)	Group 2 (n = 33)	Group 3 (n = 39)	Group 4 (n = 39)
Male, no. (%)	6 (54.5)	19 (57.6)	23 (58.9)	20 (51.3)
Age, y	15 (8–26)	13 (11–17)	13 (10–15)	14 (11–17)
Height, cm	160 (130–166)	159 (140–165)	153 (135–162)	156 (138–168)
Weight, kg	52 (32–61)	48 (36–61)	48 (31–58)	44 (34–55)
Body mass index Z score*	0.81 (0.10–1.22)	0.04 (−0.61–0.87)	0.29 (−0.15–1.07)	−0.13 (−0.88–0.15)†
Midarm muscle circumference, cm*	24 (21–27)	23 (19–25)	23 (20–25)	20 (17–22)‡
Triceps skinfold thickness, mm*	13 (9–15)	13 (8–15)	12 (10–17)	11 (7–13)§
Upper-arm muscle area, mm^2*	2754 (2111–3359)	2678 (2063–3522)	2603 (1784–3257)	2219 (1578–2670)‡
FVC, % predicted	112 (81–125)	105 (96–115)	109 (90–119)	96 (74–112)
FEV_1, % predicted	107 (88–125)	99 (80–118)	99 (72–124)	95 (63–116)
$MEF_{25–75}$, % predicted	98 (70–124)	71 (47–102)	78 (39–115)	68 (34–105)
Breathing frequency, breaths/min	18 (16–19)	17 (15–22)	16 (15–21)	19 (16–23)
Tidal volume, L	0.72 (0.37–0.82)	0.52 (0.41–0.62)	0.48 (0.37–0.70)	0.48 (0.36–0.69)
Tidal volume, mL/kg	13.9 (6.0–17.1)	10.9 (8.8–14.7)	10.3 (7.7–14.8)	10.3 (8.8–14.0)
Minute ventilation, L/min	8.64 (7.22–13.68)	9.69 (7.25–11.03)	8.63 (6.56–11.33)	9.31 (6.80–11.52)
Inspiratory flow, L/s	0.323 (0.255–0.525)	0.344 (0.282–0.435)	0.318 (0.270–0.408)	0.350 (0.257–0.427)
T_I, s	1.49 (1.22–1.52)	1.50 (1.20–1.84)	1.53 (1.31–1.84)	1.39 (1.10–1.56)
T_{tot}, s	3.29 (3.06–3.56)	3.37 (2.65–4.16)	3.40 (2.82–4.16)	3.15 (2.62–3.64)
T_I/T_{tot}	0.45 (0.43–0.47)	0.44 (0.42–0.47)	0.45 (0.43–0.47)	0.44 (0.41–0.46)
$P_{0.1}$, cm H_2O	2.18 (1.37–3.74)	2.28 (1.78–3.04)	2.51 (1.76–3.88)	2.76 (1.95–3.91)
Inspiratory pressures				
Mean, cm H_2O	17.8 (8.9–24.9)	17.9 (12.9–24.5)	18.6 (13.5–26.4)	20.5 (13.2–28.4)
Maximum, cm H_2O*	86 (56–103)	74 (62–93)	72 (55–97)	62 (48–78)‡
Maximum, % predicted*	100 (82–124)	96 (85–123)	99 (85–126)	82 (63–114)§
Mean/maximum*	0.208 (0.137–0.307)	0.220 (0.146–0.335)	0.261 (0.179–0.376)	0.317 (0.213–0.460)‖
Pressure-time index of the respiratory muscles*	0.097 (0.067–0.131)	0.102 (0.063–0.149)	0.116 (0.080–0.175)	0.142 (0.097–0.190)‖
Expiratory pressures				
Maximum, cm H_2O	71 (50–108)	75 (50–95)	66 (49–96)	62 (46–84)
Maximum, % predicted	69 (60–119)	75 (59–89)	78 (57–101)	69 (51–80)

Values are median (IQR) unless otherwise indicated.
* $P < .05$ via Kruskal-Wallis test, for differences between the *P. aeruginosa* groups.
† $P < .05$ via Mann-Whitney post hoc test for group 4 versus groups 1 and 3.
‡ $P < .05$ via Mann-Whitney post hoc test for group 4 versus all other groups.
§ $P < .05$ via Mann-Whitney post hoc test for group 4 versus groups 2 and 3.
‖ $P = .01$ via Mann-Whitney post hoc test for group 4 versus group 2.
$MEF_{25–75}$ = maximum expiratory flow during the middle half of the FVC maneuver
T_I = inspiratory time
T_{tot} = total breathing cycle time
$P_{0.1}$ = airway-occlusion pressure 0.1 s after the start of inspiratory flow

weakness via "spill-over" of inflammatory mediators. Pulmonary inflammation and consequent injury is linked to systemic inflammation in patients with COPD,[29] and increased circulating inflammatory markers have been detected in CF subjects.[30,31] Infection induces respiratory muscle weakness in animal models,[32] and respiratory muscle weakness is associated with upper-respiratory-tract infections in humans.[33] Induced chronic bronchopulmonary infection by *P. aeruginosa* significantly decreased diaphragm and limb strength in infected mice,[28] and tumor necrosis factor alpha depressed the diaphragmatic tetanic force in murine diaphragm and limb muscle preparations.[8] Furthermore, in mice, endotoxin caused diaphragm weakness and contractile dysfunction.[34]

Respiratory muscle function is compromised in CF, according to some studies, which reported decreased maximal respiratory pressures in hyperinflated, malnourished CF patients with airway obstruction.[13-15,35] PTI_{mus} was abnormal in CF patients, indicating respiratory muscle impairment related to nutritional compromise, decreased somatic muscle mass, hyperinflation, and airway obstruction.[13-15]

In our study, PTI_{mus} was selected to describe respiratory muscle function because it is measured noninvasively and it is a global respiratory-muscles index that incorporates properties of time, respiratory load, and neuromuscular competence.[20] As a limitation of PTI_{mus} in CF we should mention that measurement of $P_{0.1}$ might be affected by the

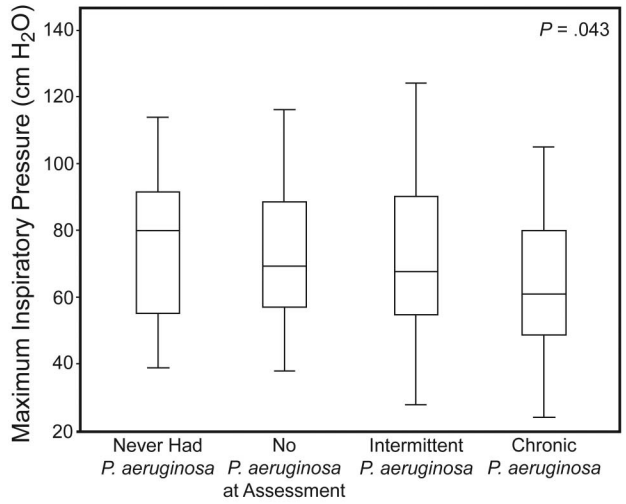

Fig. 1. Maximum inspiratory pressure in 4 subgroups of patients with cystic fibrosis. In each data bar the horizontal line represents the median, the bottoms and tops of the bars represent the 25th and 75th percentiles, and the whisker bars represent the 5th and 95th percentiles. $P = .043$ for the comparison of all the groups.

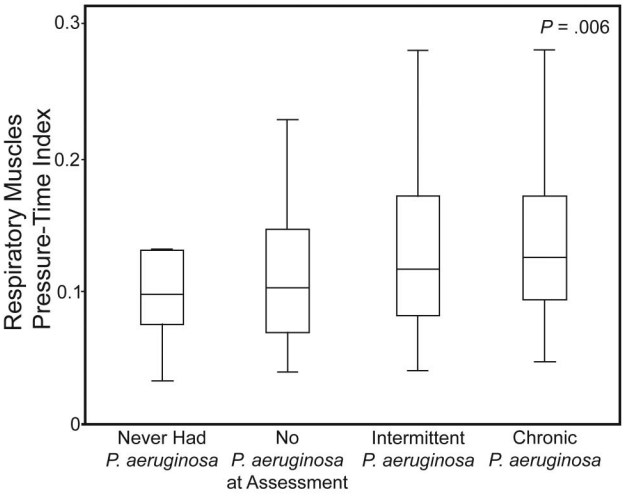

Fig. 2. Pressure-time index of the respiratory muscles in 4 subgroups of patients with cystic fibrosis. In each data bar the horizontal line represents the median, the bottoms and tops of the bars represent the 25th and 75th percentiles, and the whisker bars represent the 5th and 95th percentiles. $P = .006$ for the comparison of all the groups.

increased time-constant of the CF lung and the ensuing delayed transmission of the pressure changes from the alveoli to the mouth, as exhibited in COPD subjects.[36] Sniff nasal inspiratory pressure has been proposed as an alternative noninvasive test of respiratory muscle function in CF, but nasal inspiratory pressure underestimates esophageal pressure, probably because of nasal obstruction and dampening of the pressure changes secondary to the increased time-constant of the CF lung.[37]

Table 2. Multivariate Logistic Regression Analysis With Pressure-Time Index of the Respiratory Muscles as the Outcome Variable

	95% CI	Standardized Coefficient	*P*
FEV_1, % predicted	0.000 to 0.000	−0.128	.17
Upper-arm muscle area	0.000 to 0.000	−0.087	.37
Sex	−0.043 to 0.009	−0.120	.20
P. aeruginosa infection state	0.002 to 0.029	0.210	.03

BMI Z score, midarm muscle circumference, and upper-arm muscle area were significantly decreased in our CF subjects with chronic *P. aeruginosa* infection. Muscular indices and lean body mass correlate well with respiratory muscle indices.[15] It has been suggested that decreased muscular synthesis and impaired muscle regeneration occur in the presence of abundant pro-inflammatory cytokines in the chronically infected lung, which spill over and cause chronic systemic inflammation.[38]

Recent work addressed sex differences in the course of *P. aeruginosa* infection in patients with CF, and highlighted that estrogen induces mucoid conversion of *P. aeruginosa* in women with CF and is associated with more frequent exacerbations.[6] On the other hand, male CF patients with impaired skeletal muscle strength have normal testosterone levels.[39] Mucoid conversion of *P. aeruginosa* in CF is associated with resistance to antibiotics and increased morbidity and mortality.[40] In the present study, which was not designed to address those questions, sex and the mucoid state of *P. aeruginosa* were not significant determinants of respiratory muscle function in CF subjects. The lack of statistical difference in P_{Imax} between subjects infected with mucoid versus non-mucoid *P. aeruginosa* raises the question of whether muscle weakness is the result of the chronic disease itself rather than the *P. aeruginosa* infection state. Of note, P_{Imax} in CF subjects chronically infected with the non-mucoid strain was nonsignificantly higher than in CF subjects chronically infected with the mucoid strain. This might represent the course of disease progression in CF, reflecting mucoid-strain conversion and increasing disease severity with age.

Compared to previous studies, our study reports similar maximal respiratory pressure and PTI_{mus} values. P_{Emax} was not significantly different between the 4 subgroups, which might indicate a preferential action of chronic *P. aeruginosa* infection on the diaphragm rather than on the expiratory muscles, which might be explained by way of proximity. A preferential-to-the-diaphragm weakness was demonstrated in induced sustained *P. aeruginosa* infection in animal models.[28]

Our subjects had good lung function, probably due to idiosyncratic reasons. This was not deliberately done, although enrollment was limited to stable out-patients. Fur-

thermore, our study included younger subjects than have previous studies,[14,15,38] who probably (due to limited disease progression) had milder lung disease, implying that further investigation in older CF patients with lower baseline lung function may demonstrate an even more pronounced effect.

Adult CF patients with severe lung disease have increased diaphragm thickness and inspiratory strength,[38] probably as a result of the training effect that the chronically increased respiratory load imposes on the respiratory muscles. In these patients inflammation was not identified as a predictor of respiratory muscle compromise, whereas fat-free mass and airway resistance were.[38] In our cohort of CF subjects with mild lung disease, diaphragm thickening might have not yet occurred, and the respiratory muscles might have been exposed to the deleterious effects of chronic infection and malnutrition in the absence of a counterbalancing diaphragm thickening mechanism.

Limitations

At present, no definition of chronic *P. aeruginosa* infection has been universally accepted. In keeping with defining chronic infection as an infectious process that persists despite appropriate therapy, chronic infection could be more accurately described by persistent pathological and immune marker abnormalities.[26] Due to technical limitations we were unable to collect data on functional residual capacity, precluding the possibility of incorporating hyperinflation as another factor that probably contributes to respiratory muscle impairment in CF, as suggested in previous studies.[14,15] Furthermore, it is possible that the lack of lung-function and breathing-cycle differences between the groups was largely because all our subjects were in good pulmonary condition, and if more debilitated subjects had been included more differences might have emerged. We acknowledge this as a probable bias, since CF subjects with more severe lung disease could have respiratory muscle impairment secondary to marked airway obstruction and hyperinflation, on top of the impairment caused by chronic *P. aeruginosa* infection. Thus, our selection of a mildly lung-function-impaired cohort might have affected the results and their applicability in the CF community. Finally, although subjects with various other pathogens were excluded, for logistical reasons we did not exclude subjects infected with *S. aureus* or *H. influenzae*, because such a cohort could not be empowered for statistical analysis, nor did we apply polymerase-chain-reaction testing in the assessment of sputum samples. Therefore the contribution of *S. aureus* and *H. influenzae* to our results cannot be safely refuted; however, in practical terms, obtaining enough patients for such a cohort would be very challenging for any CF center. Although it is possible that co-infected CF subjects have worse outcomes, both *S. aureus* and *H. influenzae* are frequently found early on in CF patients, and their contribution to CF lung-disease progression and respiratory muscle impairment has not been clearly delineated.

Clinical Applicability

Identifying chronic *P. aeruginosa* infection as an independent predictor of respiratory muscle compromise implies that aggressive eradication of *P. aeruginosa* might help delay respiratory muscle fatigue and respiratory failure in patients with CF. Patients chronically infected with *P. aeruginosa* could be targeted for respiratory muscle function testing, especially if they have other risk factors, such as malnutrition, hyperinflation, or airway obstruction. Treatments that alleviate respiratory load and decrease the work of breathing, such as noninvasive ventilation,[41] inspiratory muscle training, and aerobic exercise, could then be initiated on the basis of the respiratory muscle function condition.

Conclusions

CF patients with chronic *P. aeruginosa* infection had impaired respiratory muscle function. Maximal inspiratory pressure was significantly lower and PTI_{mus} was significantly higher in CF subjects with chronic *P. aeruginosa* infection than in those without chronic *P. aeruginosa* infection. Midarm muscle circumference and upper-arm muscle area were significantly lower in subjects with chronic *P. aeruginosa* infection than in subjects who had never been infected, were currently free of infection, or had intermittent infection with *P. aeruginosa*. Chronic *P. aeruginosa* infection might be an independent determinant of respiratory muscle compromise in patients with CF.

ACKNOWLEDGMENTS

We thank Richard Parker PhD, Centre for Applied Medical Statistics, University of Cambridge, United Kingdom, for assistance with the statistical analysis.

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