Impact of *Pseudomonas aeruginosa* Infection on Respiratory Muscle Function in Adult Cystic Fibrosis Patients

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Keywords

Cystic fibrosis · *Pseudomonas aeruginosa* · Respiratory muscle function · Respiratory muscle physiopathology · Quality of Life

Abstract

Background: *Pseudomonas aeruginosa* infection impairs respiratory muscle function in adolescents with cystic fibrosis, but its impact on adult patients has not been characterised. **Objectives:** To investigate respiratory muscle function in adult cystic fibrosis patients according to *P. aeruginosa* status (repetitive samples over 12 months). **Methods:** The pressure-time index of the respiratory muscles (PTI_{mus}), a measure of their efficiency, served as the primary outcome. In addition, respiratory load and maximal respiratory muscle strength were assessed. **Results:** In 51 patients examined (65% female; median age 32 years, IQR 24–40), a median of 3.0 (IQR 2–4) different pathogens was found in each patient. The PTI_{mus} was 0.113 and 0.126 in *Pseudomonas*-positive ($n = 33$) and -negative ($n = 18$) patients, respectively ($p = 0.53$). Univariate analysis showed a lower PTI_{mus} in male than in female patients ($p = 0.006$). Respiratory muscle load

and strength were otherwise comparable, with the exception of higher nasal sniff pressures in *Pseudomonas*-positive patients who were chronically infected (>50% of positive samples). Quality of Life (according to the Cystic Fibrosis Questionnaire-Revised) was higher if both respiratory load and the PTI_{mus} were low (high respiratory muscle efficiency). **Conclusions:** Chronic *P. aeruginosa* infection does not influence respiratory muscle efficiency in adult cystic fibrosis patients with otherwise multiple co-infections. In addition, patients with reduced respiratory muscle efficiency had worse Quality of Life.

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Introduction

The median life expectancy in cystic fibrosis (CF) patients has increased in the last decades and is estimated to be >50 years in children who were born after the year 2000 [1]. However, *Pseudomonas aeruginosa* infection in CF patients remains a major problem, with a negative impact both on overall survival and Quality of Life (QoL) [2–4].

In this regard, respiratory disturbances related to *P. aeruginosa* infection are a major predictor of morbidity and mortality amongst CF patients [3]. These disturbances may affect the lungs, as well as respiratory mechanics, where the presence of both conditions can contribute to dyspnoea and may ultimately lead to respiratory failure. Furthermore, chronic *P. aeruginosa* infection and high IgG levels were shown to be associated with a decline in exercise capacity in adolescent patients with CF [5], and a decreased exercise capacity is found in a relevant proportion of patients with CF [6]. Despite the link between *P. aeruginosa* infection and respiratory disturbances, respiratory mechanics are rarely investigated in CF patients. In general, the load imposed on the respiratory muscles, respiratory muscle efficiency, and respiratory muscle strength are all key factors in determining respiratory mechanics [7]. In particular, the impact of *P. aeruginosa* infection on respiratory mechanics is not fully understood, but it is suggested to be clinically important, since chronic infection has been shown to impair respiratory muscle function [8]. Importantly, an animal study showed that CF mice with sustained infection with *P. aeruginosa* had a reduced diaphragmatic force-generating capacity [9]. Furthermore, a detailed study on the impact of *P. aeruginosa* infection on respiratory mechanics in adolescent CF patients clearly showed that *P. aeruginosa* infection can indeed have an independent effect on respiratory muscle function [7].

However, the findings reported in that study are only valid for adolescents, since the median age of the subjects was 13 years (IQR 10–17). In contrast to their younger counterparts, adult CF patients have (1) different as well as additional co-morbidities, (2) a longer disease duration, and (3) co-existing infections. Therefore, the impact of *P. aeruginosa* infection on respiratory muscle function needs to be elucidated specifically for adult patients. As a consequence, the present study aimed to carry out a detailed characterisation of respiratory muscle function in adult CF patients while simultaneously investigating the impact of *P. aeruginosa* infection on respiratory mechanics.

Patients and Methods

The study protocol was approved by the Ethics Committee at Witten/Herdecke University, Witten, Germany, and was undertaken at the Department of Pneumology of the Lung Clinic, Cologne Merheim Hospital, Witten/Herdecke University, Cologne, Germany. The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki (last revision

from October 2013). The study was registered at the German Clinical Trials Register (DRKS00008786). Informed written consent was obtained from all subjects.

Patients

Adult outpatients (≥ 18 years of age) with an established diagnosis of CF according to guidelines [10] were included in the study. All subjects were in a stable disease state. Patients were excluded from the study if any of the following criteria were met:

- Pulmonary exacerbation (as previously defined [11]), with or without hospitalisation, within 30 days of study uptake
- Hospitalisation due to any cause other than exacerbation within 30 days of study uptake
- Administration of intravenous antibiotics within 30 days of study uptake
- Status post lung transplantation

Respiratory Muscle Assessment, Lung Function Testing, and Exercise Capacity Assessment

Respiratory muscle function parameters were assessed using the ZAN 100 (nSpire, Oberthulba, Germany). Specifically, the following measurements were performed: nasal sniff pressures ($Sn_{P_{na}}$); the pressure generated in the first 100 ms of inspiration against an occluded airway during quiet breathing ($P_{0.1}$); maximum inspiratory mouth occlusion pressure (PI_{max}); maximum expiratory mouth occlusion pressure (PE_{max}); tidal volume (TV); breathing frequency (Bf); minute ventilation; total cycling time (T_{tot}); and inspiratory time (T_I). All measurements were performed in accordance with the recent German recommendations for respiratory muscle testing [12], which conform to international guidelines [13]. The only difference pertained to the measurement of PI_{max} , which was assessed as peak pressure at residual volume. Importantly, previous research has clearly shown that this is a comparable, reliable approach to the assessment of inspiratory muscle strength when compared to plateau pressures obtained according to international guidelines [14].

From these measurements, the following calculations were performed: respiratory capacity ($P_{0.1}/PI_{max}$) and specific inspiratory impedance ($P_{0.1} \times T_I/TV$), where each served as a surrogate for respiratory load, and airway pressure during inspiration ($P_I = 5 \times P_{0.1} \times T_I$ [15–17]). Finally, the pressure-time index of the respiratory muscles (PTI_{mus}) was calculated as follows: $PTI_{mus} = (\text{mean } P_I/PI_{max}) \times (T_I/T_{tot})$. PTI_{mus} is suggested to represent the balance between neuromuscular competence and respiratory load, as well as the efficiency of the respiratory muscles [7, 15, 16]. In this regard, a higher PTI_{mus} indicates ineffective or limited respiratory muscle function, and is associated with a higher risk of respiratory muscle fatigue [7, 17].

Lung function parameters were assessed in accordance with international guidelines (spirometry and full body plethysmography; ZAN 500; nSpire) [18–22]. In addition, the standardised 6-min walk test (6MWT) was performed according to previous recommendations [23, 24]. Here, capillary blood gas analysis was additionally performed prior to and directly after walking [25].

QoL Measurements

QoL was assessed using the Cystic Fibrosis Questionnaire-Revised (CFQ-R) [26, 27]. The CFQ-R contains 12 domains (scores ranging from 0 to 100), where higher scores represent a better QoL. For further analysis, 4 of the 12 subscales suitable according to the

Table 1. Demographic and quality-of-life data (CFQ-R) for the 8 infection status groups

	Group 1 (n = 13)	Group 2 (n = 5)	Group 3 (n = 5)	Group 4 (n = 28)
Male, n (%)	3 (23.1)	2 (40.0)	1 (20.0)	12 (42.9)
BMI	24.7 (21.1–26.5)	22.2 (19.6–22.3)	20.2 (18.1–21.7)	21.7 (19.7–23.9)
Age, years	27.0 (23.0–35.0)	30.0 (25.0–37.0)	32.0 (30.0–32.0)	32.5 (25.0–46.0)
CFQ-R subscale score				
Physical functioning	70.8 (57.1–95.8)	87.5 (75.0–95.8)	91.7 (79.2–91.7)	81.3 (62.5–87.5)
Respiratory symptoms	72.2 (61.1–83.3)	61.1 (50.0–66.7)	61.1 (44.4–77.8)	61.1 (54.4–75.6)
Health perception	66.7 (55.6–88.9)	66.7 (55.6–77.8)	66.7 (55.6–77.8)	66.7 (55.6–88.9)
Treatment burden	55.6 (33.3–77.8)	66.7 (44.4–66.7)	66.7 (44.4–88.9)	66.7 (55.6–77.8)
	Group A (n = 18)	Group B (n = 33)	Group C (n = 23)	Group D (n = 28)
Male, n (%)	5 (27.8)	13 (39.4)	6 (26.1)	12 (42.9)
BMI	22.6 (20.7–25.5)	21.6 (19.7–23.6)	22.1 (19.6–25.1)	21.7 (19.7–23.9)
Age, years	28.5 (24.0–37.0)	32.0 (26.0–40.0)	30.0 (24.0–37.0)	32.5 (25.0–46.0)
CFQ-R subscale score				
Physical functioning	81.3 (58.3–95.8)	83.3 (66.7–91.7)	87.5 (58.3–95.8)	81.3 (62.5–87.5)
Respiratory symptoms	69.5 (50.0–83.3)	61.1 (53.3–77.8)	66.7 (50.0–77.8)	61.1 (54.4–75.6)
Health perception	66.7 (55.6–88.9)	66.7 (55.6–88.9)	66.7 (55.6–88.9)	66.7 (55.6–88.9)
Treatment burden	61.2 (44.4–77.8)	66.7 (55.6–77.8)	66.7 (44.4–88.9)	66.7 (55.6–77.8)

Values are indicated as median (and IQR). Groups according to *Pseudomonas aeruginosa* status (Leeds criteria [29]): group 1 = never infected; group 2 = free of infection; group 3 = intermittently infected; group 4 = chronically infected. Group A = comprising groups 1 and 2 (*P. aeruginosa* negative); group B = comprising groups 3 and 4 (*P. aeruginosa* positive); group C = comprising groups 1, 2, and 3 (not chronically infected with *P. aeruginosa*); group D = comprising group 4 (chronically infected with *P. aeruginosa*). CFQ-R, Cystic Fibrosis Questionnaire-Revised; IQR, interquartile range.

content of the subscale were used to determine the effect of *P. aeruginosa* infection on respiratory muscle function: treatment burden, health perception, physical functioning, and respiratory symptoms.

Study Design

Patients were recruited during a routine outpatient visit. QoL was assessed first, followed by blood gas measurements during rest. Next, lung function and respiratory muscle function were assessed. Finally, the 6MWT was performed.

For microbiological assessment, sputum from expectorating patients was used. If patients could not sufficiently produce sputum, a deep cough swab was used [28]. Samples were collected in sterile disposable tubes, stored at room temperature, and then inoculated and incubated for 10 days for further analysis. For additional classification, both the current microbiological samples and all available past samples were analysed. As clinical routine, microbiological samples were taken at least every 12 weeks.

Classification of *P. aeruginosa* Infection Status

The Leeds criteria were used to classify *P. aeruginosa* infection status [29]. Accordingly, patients were classified as (1) “never infected” if *P. aeruginosa* had never been cultured (group 1), (2) “free of infection” if the samples were negative for ≥ 12 months following a positive culture test (group 2), (3) “intermittently infected” if $\leq 50\%$ of the samples were positive for *P. aeruginosa* (group 3), and (4) “chronically infected” if $>50\%$ of the samples were positive for *P. aeruginosa* (group 4).

For the final analysis, group A (comprising groups 1 and 2; “*P. aeruginosa* negative”) was compared to group B (comprising groups 3 and 4; “*P. aeruginosa* positive”). Furthermore, in a different analysis, group C (comprising groups 1, 2, and 3; “not chronically infected with *P. aeruginosa*”) was compared to group D (comprising group 4; “chronically infected with *P. aeruginosa*”).

Statistical Analysis

The primary objective of the study was to compare groups A and B (see Classification of *P. aeruginosa* Infection Status) with respect to the primary endpoint PTI_{mus}, and to investigate whether *P. aeruginosa* infection status affected respiratory muscle function in adult CF patients. About 50 patients were screened for recruitment, and we assumed they would divide equally into 2 groups. Based on previous work by Dassios et al. [7], a normal distribution was assumed for PTI_{mus}, with a standard deviation (SD) of 0.06. Therefore, the study had a power of 80% to detect a difference in PTI_{mus} according to the status of *P. aeruginosa* infection, with a 2-sided significance level α of 5% if the difference was 0.05. This difference was assumed to be clinically relevant and realistic.

A 2-sided *t* test was performed at a 2-sided α level of 5%, and the difference between groups was calculated with a 95% confidence interval (CI). Furthermore, the influence of *P. aeruginosa* infection status on PTI_{mus} was examined in a linear regression model, in which other baseline factors with influences on PTI_{mus} were added for adjustment.

Table 2. Pulmonary and respiratory muscle function as well as IgG levels for the 4 infection status groups

	Group 1 (n = 13)	Group 2 (n = 5)	Group 3 (n = 5)	Group 4 (n = 28)
Lung function				
FEV ₁ , %pred.	80 (50–90)	71 (56–72)	78 (48–99)	63 (52–73)
TLC, %pred.	98 (89–112)	110 (99–114)	118 (108–122)	108 (101–118)
RV, %pred.	137 (115–173)	132 (84–163)	172 (148–249)	164 (136–201)
RV/TLC, %	39 (36–46)	44 (33–44)	37 (37–53)	45 (38–54)
IVC, %pred.	84 (68–99)	92 (81–101)	91 (71–100)	83 (68–90)
Blood gases				
pH	7.42 (7.41–7.43)	7.42 (7.41–7.45)	7.41 (7.41–7.42)	7.42 (7.41–7.43)
PaCO ₂	36.7 (34.2–37.0)	34.8 (33.9–36.6)	38.9 (34.4–39.8)	36.5 (35.3–38.1)
PaO ₂	83.0 (79.2–84.6)	81.9 (78.0–84.1)	81.2 (72.3–91.2)	77.5 (70.5–83.3)
HCO ₃ ⁻	24.1 (23.2–24.6)	23.7 (22.6–24.8)	24.5 (22.8–25.1)	23.9 (23.3–24.7)
SaO ₂	97.0 (96.7–97.4)	97.0 (96.7–97.3)	96.5 (95.7–96.7)	96.3 (95.6–97.0)
6MWT				
Distance, m	543 (528–637)	632 (562–648)	612 (590–629)	604 (548–643)
Respiratory muscle function				
P _{0.1} , kPa	0.26 (0.20–0.40)	0.30 (0.17–0.31)	0.24 (0.20–0.28)	0.29 (0.23–0.38)
PI _{max} , kPa	8.7 (6.0–10.8)	8.8 (6.5–13.3)	9.6 (7.6–10.6)	9.1 (7.2–11.2)
PE _{max} , kPa	11.4 (8.7–13.2)	10.2 (7.6–14.2)	11.0 (10.6–11.1)	10.3 (8.4–15.1)
P _{0.1} × T _I /TV	0.5 (0.4–0.6)	0.5 (0.5–0.6)	0.4 (0.3–0.6)	0.5 (0.5–0.8)
PTI _{mus}	0.130 (0.097–0.150)	0.074 (0.044–0.116)	0.083 (0.065–0.092)	0.096 (0.074–0.156)
P _{0.1} /PI _{max} , %	4 (3–5)	2 (2–5)	2 (2–2)	3 (2–6)
Sn _{pna} , kPa	5.2 (3.8–6.3)	4.7 (2.6–6.3)	4.8 (2.8–6.4)	5.8 (5.1–8.4)
Immunoglobulin				
IgG level, g/L	13.0 (11.6–15.8)	12.0 (11.9–15.4)	12.9 (10.9–13.5)	14.3 (12.4–16.8)

Values are indicated as median (and IQR). FEV₁, forced expiratory volume in 1 s; HCO₃⁻, bicarbonate; IgG level, level of immunoglobulin G (normal value 7–16 g/L); IQR, interquartile range; IVC, inspiratory vital capacity; PaCO₂, arterial pressure of carbon dioxide; PaO₂, arterial pressure of oxygen; PE_{max}, maximum expiratory mouth occlusion pressure; PI_{max}, maximum inspiratory mouth occlusion pressure; PTI_{mus}, pressure-time index of the respiratory muscles; P_{0.1}, decrease in airway pressure at 0.1 s; P_{0.1} × T_I/TV, specific inspiratory impedance; P_{0.1}/PI_{max}, respiratory capacity; RV, residual volume; SaO₂, oxygen saturation; Sn_{pna}, nasal sniff pressures; TLC, total lung capacity; 6MWT, standardised 6-min walk test.

Secondary endpoints were lung function assessment, 6MWT (m), respiratory muscle function parameters (PI_{max}, PE_{max}, P_{0.1}, Sn_{pna}, respiratory capacity [P_{0.1}/PI_{max}], and the effective inspiratory impedance [P_{0.1} × T_I/TV]), and QoL data. Comparisons of the infection status groups with respect to the secondary endpoints were performed with the same methods. Spearman correlation coefficients were calculated to describe the associations between primary and secondary endpoints. All *p* values of secondary analyses had to be interpreted descriptively.

Results

Fifty-one patients (33 female = 64.7%) were consecutively enrolled in the study from July to November 2015. Their median age, BMI, and percentage-of-predicted (%pred.) FEV₁ was 32 years (IQR 24–40), 22.0 (IQR 19.7–24.2), and 66% (IQR 51–83), respectively. There were at least 4 microbiological samples per patient; 9 patients

(17.6%) had deep cough swabs instead of sputum samples for microbiological assessment, and 4 out of those patients were chronically infected with *P. aeruginosa* (group 4). A total of 36 different pathogens (including bacteria, fungi, and mycobacteria) were found across all microbiological samples of the study population, ranging from 0 to 7 different pathogens per individual patient (median 3.0 per patient, IQR 2–4). The most frequently found pathogen was *P. aeruginosa* (*n* = 35), followed by *Staphylococcus aureus* (*n* = 28), *Candida albicans* (*n* = 27), and *Aspergillus fumigatus* (*n* = 10).

Four out of the 51 patients (7.8%) were on systemic steroids with 5 mg prednisolone per day: 2 patients with CF arthropathy and 2 with status post allergic bronchopulmonary aspergillosis.

The demographic and QoL data for the 8 infection status groups are shown in Table 1. The pulmonary and respiratory muscle function results as well as the IgG levels

Fig. 1. Pressure-time index of the respiratory muscles (PTI_{mus}). Group A vs. group B.

Fig. 2. Pressure-time index of the respiratory muscles (PTI_{mus}). Group C vs. group D.

Table 3. Analysis of the correlation of the PTI_{mus} and QoL subdomains with respiratory muscle function parameters, lung function, and exercise capacity

	PTI _{mus}		QoL: physical functioning		QoL: respiratory symptoms	
	<i>r</i> value	<i>p</i> value	<i>r</i> value	<i>p</i> value	<i>r</i> value	<i>p</i> value
QoL: physical functioning	−0.48	0.0004	–	–	0.63	<0.0001
QoL: respiratory symptoms	−0.42	0.002	0.63	<0.0001	–	–
P _{0.1}	0.68	<0.0001	−0.45	0.0009	−0.42	0.002
P _{0.1} × T _I /TV	0.72	<0.0001	−0.53	<0.0001	−0.41	0.0031
P _{0.1} /PI _{max}	0.92	<0.0001	−0.57	<0.0001	−0.45	0.001
PI _{max}	−0.57	<0.0001	0.36	0.009	0.27	0.055
PE _{max}	−0.52	<0.0001	0.25	0.074	0.30	0.03
Sn _{Pna}	−0.30	0.03	0.12	0.40	0.15	0.28
FEV ₁	−0.34	0.016	0.48	0.0004	0.37	0.007
6MWT	−0.29	0.04	0.19	0.18	0.14	0.34

FEV₁, forced expiratory volume in 1 s; PE_{max}, maximum expiratory mouth occlusion pressure; PI_{max}, maximum inspiratory mouth occlusion pressure; PTI_{mus}, pressure-time index of the respiratory muscles; P_{0.1}, decrease in airway pressure at 0.1 s; P_{0.1} × T_I/TV, specific inspiratory impedance; P_{0.1}/PI_{max}, respiratory capacity; Sn_{Pna}, nasal sniff pressures; QoL, Quality of Life; 6MWT, standardised 6-min walk test.

are displayed in Table 2. The median dyspnoea (BORG scale) score in the 6MWT was 0 before walking in all groups, and 0 after walking in groups 1, 3, and 4. Group 2 had a median score of 2 points after walking.

Primary Outcome Parameter (PTI_{mus})

There was no significant difference in PTI_{mus} between group A (mean 0.113, SD 0.049) and group B (mean 0.126, SD 0.080; difference 0.013, 95% CI [−0.028, 0.055]; *p* = 0.53) (Fig. 1). Further explorative evaluation showed no difference between group C (mean 0.107, SD 0.047) and group D (mean 0.133, SD 0.084; difference 0.026, 95% CI [−0.014, 0.065]; *p* = 0.20) (Fig. 2).

Multivariate analysis investigating the effects of gender, Sn_{Pna}, BMI, FEV₁ (%pred.), TLC (%pred.), and walking distance (m) showed a lower PTI_{mus} in male than in female patients (difference −0.059, 95% CI [−0.103, −0.015]; *p* = 0.010). Sn_{Pna}, BMI, FEV₁ (%pred.), TLC (%pred.), and walking distance (m) had no influence on PTI_{mus}.

There was no significant difference in PTI_{mus} in regard to normal versus elevated IgG levels (cut-off >16 g/L) (mean PTI_{mus} 0.121 [SD 0.077] vs. 0.124 [SD 0.047]; difference −0.003, 95% CI [−0.050, 0.042]; *p* = 0.89). In addition, after adjusting for other factors in this multivariate analysis, no difference could be detected between the infection status groups.

Fig. 3. Correlation analysis of the pressure-time index of the respiratory muscles (PTI_{mus}) with the Quality-of-Life (QoL) item “physical functioning.”

Fig. 4. Correlation analysis of the pressure-time index of the respiratory muscles (PTI_{mus}) with the Quality-of-Life (QoL) item “respiratory symptoms.”

Table 4. Quality-of-Life data (CFQ-R) according to gender

CFQ-R subscale	Male (n = 18)	Female (n = 33)	Difference of means	95% CI	p value
Physical functioning	89.6 (79.2–95.8)	75.0 (58.3–87.5)	12.1	0.52 to 23.60	0.041
Respiratory symptoms	75.6 (61.1–83.3)	61.1 (50.0–72.2)	12.2	2.45 to 22.00	0.015
Health perception	66.7 (55.6–100)	66.7 (55.6–77.8)	8.2	–4.33 to 20.65	0.195
Treatment burden	66.7 (66.7–88.9)	55.6 (44.4–66.7)	12.7	2.31 to 23.09	0.018

Values are indicated as median (and IQR). CRQ-R, Cystic Fibrosis Questionnaire-Revised; CI, confidence interval; IQR, interquartile range.

Secondary Outcome Parameters

There were no differences between groups (A vs. B and C vs. D) when the following measures were compared: $P_{0.1}$, PI_{max} , PE_{max} , $P_{0.1}/PI_{max}$, $P_{0.1} \times T_I/TV$, the QoL items “physical functioning” and “respiratory symptoms,” BMI, FEV_1 (%pred.), IVC (%pred.), TLC (%pred.), RV

(%pred.), and walking distance (m). Regarding Sn_{pna} , the difference was 1.54 (95% CI [–0.04, 3.12]; $p = 0.056$) for group B versus group A and 1.69 (95% CI [0.20, 3.19]; $p = 0.027$) for group D versus group C. PI_{max} was 89.5% in all CF patients compared to the 50th (median) percentiles of age-related normal values in healthy subjects [14].

An analysis of the correlation of the PTI_{mus} and QoL subdomains with respiratory muscle function parameters, lung function, and exercise capacity is displayed in Table 3. In summary, PTI_{mus} was positively correlated with parameters of the load imposed on the respiratory muscles. In contrast, PTI_{mus} was negatively correlated with the parameters of inspiratory muscle strength and QoL (Fig. 3, 4). Male patients had a better QoL than female patients (Table 4).

Discussion

This is the first study to evaluate respiratory muscle function in adult CF patients in relation to *P. aeruginosa* infection status. By comparing PTI_{mus} measurements in CF patients with or without *P. aeruginosa* infection, the main finding of the present study was that there was no significant difference in the efficiency as well as the function of respiratory muscles between these 2 groups. In addition, neither the load imposed on the respiratory muscles nor the maximum inspiratory muscle strength was impaired in patients with *P. aeruginosa* infection compared to those without. In contrast, patients chronically infected with *P. aeruginosa* had greater diaphragmatic muscle strength than those patients who were not chronically infected.

The findings of the present study are in clear contrast to those of Dassios et al. [7], who investigated respiratory muscle function in adolescent CF patients according to *P. aeruginosa* infection status. Of note, that study used the same primary outcome as the present study – namely, PTI_{mus} measurement – and has been the only study to date to investigate respiratory muscle function in CF patients with respect to their *P. aeruginosa* infection status. The present report, therefore, demonstrates that the findings described for adolescent CF patients cannot be extrapolated to adult CF patients. For example, respiratory muscle efficiency was shown to be significantly impaired in adolescent CF patients with chronic *P. aeruginosa* infection, while it remained unaffected in the adult CF patients [7]. Similarly, PI_{max} measurements showed that chronic *P. aeruginosa* infection led to an impairment of global respiratory muscle strength in adolescents, whereas in adults it did not. Furthermore, diaphragmatic strength was found to be rather greater in chronically affected adult patients. Increased respiratory muscle strength has previously been attributed to a training effect that is related to the increased work of breathing [30]; this is also true for chronic *P. aeruginosa* infection. However,

there are conflicting results regarding respiratory muscle strength in the literature [30–33], and this issue needs to be elucidated in the future.

The reasons for these discrepancies between study findings remain unclear, but they seem to be complex. One possible explanation is that respiratory muscle function in older patients with a longer history of CF, more co-morbidities, other treatment strategies, or additional respiratory affection is influenced by more than just *P. aeruginosa* infection alone. In this regard, the present study provided detailed information on the presence of other pathogens, showing that most of the patients had multiple co-infections. Importantly, such information was omitted from the study by Dassios et al. [7], where infection with pathogens other than *P. aeruginosa* (with the exception of *Haemophilus influenzae* and *S. aureus*) led to exclusion from the study.

Importantly, the respiratory muscle function parameters showed broad variability, particularly in the case of efficiency, load, and strength. In addition, respiratory muscle function was more efficient in male than in female patients. This could be explained by the greater global inspiratory muscle strength in males [14], which is included in the calculation of the PTI_{mus}. Correspondingly, male patients showed a higher QoL than female patients.

In addition, some patients were hyperinflated, and this could also have led to an impairment of respiratory muscle strength, as has previously been shown in patients with CF [31]. However, the degree of hyperinflation was mild, and only severe hyperinflation as defined by an RV/TLC ratio >50% was shown to be associated with impaired respiratory muscle strength [31]. Moreover, there was no clear difference between the subgroups of patients regarding the degree of hyperinflation.

However, other conditions predisposing respiratory muscle function to impairment remain unclear. To this end, the present study showed that reduced efficiency of the respiratory muscles was associated with reduced QoL. In addition, QoL was suggested to be lower in patients never infected with *P. aeruginosa*, even though the opposite could have been expected. The reason for this, however, remains unclear. Therefore, future studies should investigate the additional factors contributing to respiratory muscle dysfunction and QoL.

There are some limitations of the study that need to be addressed. Firstly, this was a single-centre study; therefore, recruitment of patients was restricted to the group forming the outpatient pool at the CF centre. Even though the target sample size was reached, the 4

groups of patients formed according to their *P. aeruginosa* status were not equally distributed. In particular, it was difficult to find adult patients who were purely *P. aeruginosa* negative. This was completely different to the above-cited study on adolescents [7]. Secondly, many patients had co-infections with other specimens, which was not avoidable in the current adult population. Nevertheless, the impact of *P. aeruginosa* on respiratory muscle function may be misconstrued due to other pathogens contributing to changes in respiratory mechanics. Thirdly, as in all the other studies, respiratory muscle strength was measured by volitional tests, which extensively depend on participants making a truly maximal effort. However, reliable measurements would require non-volitional tests; therefore, this needs to be addressed in future studies.

In conclusion, chronic *P. aeruginosa* infection does not have an impact on respiratory muscle efficiency in adult CF patients with otherwise multiple co-infections with different specimens typical of this collective. However, respiratory muscle function was heterogeneous amongst the different CF individuals, and those CF patients with reduced respiratory muscle efficiency had worse QoL.

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