Case report

Individualized physical training in the therapy of Primary Ciliary Dyskinesia – A case report

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A B S T R A C T

Background: Primary Ciliary Dyskinesia (PCD) is an autosomal recessive disease, characterized by ciliary dysfunction and impaired mucociliary clearance. Previous studies have indicated a low physical fitness in PCD patients but currently it is not known whether physical training beneficially affects fitness, inflammatory markers and quality of life.
Case presentation: The patient was a Caucasian male (67.0 kg, 183.3 cm), born in 1984 and was diagnosed with the Kartagener Syndrome (i.e. PCD) right after birth. He was prescribed structured physical training over a period of almost two years (from August 2017–June 2019) and was assessed regularly. Aerobic fitness improved throughout the intervention period, but no systematic changes were observed in inflammatory markers and overall quality of life.
Conclusions: Our data provides reasoning to stress the implementation of structured physical training to enhance physical performance also in the management of PCD.

1. Background

Primary Ciliary Dyskinesia (PCD) is known as an autosomal recessive disease, characterized by ciliary dysfunction and impaired mucociliary clearance [3,4]. The major clinical manifestations of PCD are similar to that observed with cystic fibrosis (CF) and include upper and lower respiratory tract infections, such as chronic bronchitis, chronic rhino-sinusitis and chronic otitis [14]. Moreover, approximately 50% of patients diagnosed with PCD also present a mirror image arrangement of the visceral organs (i.e. situs inversus) and infertility [14].

Initially, PCD became known as the Kartagener Syndrome, where the diagnosis was typically based on a triad of symptoms that included chronic sinusitis, bronchiectasis and situs inversus [11,14]. Later, it was discovered that the majority of cilia are immotile but exhibit a stiff and uncoordinated movement. Thus, the name was changed to PCD to more appropriately describe the heterogeneous genetic base of the disease and to distinguish it from secondary ciliary defects induced by epithelial injury [14].

The first cases of PCD were reported in the early 1900's and the prevalence still ranges between 1:4.000 and < 1:50.000 [13]. Despite

early manifestations in the neonatal period characterized by respiratory distress [4], the mean age of PCD diagnosis is typically approximately 4 years [5]. The most common symptoms present since early infancy are persistent rhinitis and chronic cough [9]. Currently, epidemiological data describing the link between PCD and mortality are missing but PCD is generally described as being less severe when compared to CF [19]. However, impaired mucociliary clearance highly increases the risk for severe infections and, thus, decreases the quality of life and physical capabilities [14].

Despite recent progress in understanding the underlying mechanisms of the disease, the management of PCD remains difficult [12,17]. Due to a lack of long-term randomized trials on the therapy, treatment is empirically based on other chronic lung diseases, such as CF [17]. Thus, the management of PCD typically includes regular airway clearance, occasional use of antibiotics and infection control [14]. In addition, physical exercise is routinely recommended as a supportive therapy for chronic lung diseases [22,26]. Although the overall evidence for the effects of exercise in patients with CF is still low, some evidence exists for improved airway clearance [26]. Moreover, cardiopulmonary fitness assessed based on peak oxygen uptake (VO_2peak) is generally used to

predict morbidity and mortality across both healthy [23] and diseased populations, including CF [25]. Interestingly, VO_2peak obtained in cross-sectional studies of patients with PCD appears to be low compared to healthy controls [18,24]. Moreover, while in patients with asthma or CF numerous studies have demonstrated that VO_2peak can be improved through regular aerobic training [10], such data is lacking for PCD and it remains unclear as to whether these patients would benefit from other types of training (e.g. strength training) as well. Thus, it remains unclear if regular physical training leads to other health benefits, such as improved muscle strength, lung function, beneficial changes in inflammatory markers and eventually improved quality of life. Consequently, the aim of this case report was to assess whether chronic aerobic and strength training improves selected markers of health in a patient diagnosed with PCD.

2. Case presentation

The patient was a Caucasian male (67.0 kg, 183.3 cm), born in 1984 and was diagnosed with the Kartagener Syndrome (i.e. PCD) right after birth. As a result of the disease, the patient reported a chronic bronchitis (J44) and presented regular transient upper respiratory tract (J47, A49) and ear infections (H66). The patient was treated with Azithromycin (500mg) from October 2016 until April 2018 and the judicious use of Amoxicillin (875/125mg) was prescribed for severe infections. In addition, since October 2016 the patient also received regular physical respiratory therapy (3 times weekly).

Prior to inclusion into this case study, the patient was physically active, as indicated by irregular performance mainly consisting of occasional endurance running as well as mountain biking and ski touring at altitude. He contacted us for the first time in July 2017, reporting breathing difficulties concomitantly with a high heart rate during his physical activities and especially during endurance running. Consequently, we assessed his aerobic fitness in August 2017 and provided training recommendations to improve aerobic capacity. Thereafter, he was tested at the following time points: January 2018, May 2018, August 2018, February 2019 and June 2019. Assessments included a basic blood count, as well as measures of body composition, lung function, muscle strength and peak oxygen consumption (VO_2peak). In addition, from January 2018 onwards also a quality of life questionnaire was included.

The present case study was carried out in accordance with the declaration of Helsinki and received ethical approval by the Ethics Committee of the German Sport University, Cologne. The patient provided written informed consent prior to the first assessment.

3. Measurements and training

The following measurements were carried out in the order presented.

3.1. Basic blood count

Venous blood samples were collected into an EDTA-container (BD Vacutainer K2E) after an overnight fast. A basic blood count was determined by fluorescent flow cytometry (Sysmex KX-21N, Sysmex Corporation, Kobe, Japan). In addition, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and the systemic immune-inflammation index (SII, platelet counts x neutrophil counts/lymphocyte counts) were calculated. Although these novel markers have not yet been used in PCD patients, they are known from other clinical settings and may provide information on the inflammatory status [6,7,27,28].

3.2. Body composition

Body composition (total body weight and fat- and lean mass, respectively) was assessed by bioelectrical impendence (BIA, Seca medical Body Composition Analyzer (mBCA 515), seca GmbH & Co.KG.,

Hamburg, Germany), using two electrodes on the hands and feet, respectively. The body mass index (BMI) was calculated manually.

3.3. Lung function

A spirometry (Easy on-Desk, ndd Medizintechnik AG, Zurich, Switzerland) was performed to determine the mechanical function of the lung and respiratory muscles by measuring vital capacity (VC), forced vital capacity (FVC) and the forced expiratory volume in the first second of exhalation (FEV_1).

3.4. Questionnaire-assessed patient-reported outcomes

In order to assess disease-specific quality of life (QoL), the QoL-PCD questionnaire (version 2, June 2016) was used [16]. This questionnaire was specifically designed to assess quality of life in patients with PCD and includes 40 items concerning the following dimensions: "physical functioning", "vitality", "emotional functioning", "treatment burden", "role functioning", "social functioning", "health perception", "upper respiratory symptoms", "lower respiratory symptoms" and "hearing symptoms".

3.5. Maximal strength

Maximal strength was assessed by the one-repetition maximum (1RM) of the leg extensors and was determined using a dynamic horizontal leg press device (Gym80 International GmbH, Gelsenkirchen, Germany). After a standardized warm-up, a maximum of five trials was allowed to obtain a true 1RM. The device was set to obtain a knee angle in the initial flexed position of approximately 80°. A successful trial was accepted when the knees were fully extended (approximately 180°). The greatest load that the subject could lift to full knee extension at an accuracy of 2.5 kg was accepted as 1RM.

3.6. Cardiopulmonary exercise testing (CPET)

Prior to the CPET, a resting ECG was recorded and reviewed by a cardiologist. To assess VO_2peak, the patient performed an incremental CPET on a treadmill (Woodway, USA Inc.). The test started at 6 km·h^{-1} and was increased by 1 km·h^{-1} every 3 minutes until voluntary exhaustion. Following each increment, the test was stopped for 20 seconds in order to collect capillary blood samples for blood lactate assessment. In addition, breathing gases were continuously recorded breath-by-breath using a gas exchange analyser (ZAN600 CPET, nSpire Health GmbH, Oberthulba, Germany). Prior to the test, the device was calibrated for volume and fractional gas concentrations.

In order to determine blood lactate concentrations, 20 µL of capillary blood samples were collected from the earlobe within the last 20 seconds at the end of each increment (Biosen S-Line, EKF Diagnostics, Barleben, Germany). Heart rate was measured using a commercially available wrist monitor and transmitter chest belt (Polar A300 Fitness/Activity Tracker, Polar Electro, Kempele, Finland). HR readouts were reported 10 seconds prior to the end of the increment and directly after volitional termination of the CPET. Furthermore, the patient was asked to rate the subjective perceived exertion at the end of every increment on the 6–20 Borg Scale [2]. The patient was verbally encouraged to achieve maximal exhaustion.

3.7. Training recommendations

The main aim of the training prescription was to improve aerobic fitness, while during the final 4 months hypertrophic strength training was prescribed as well (leg press, leg extension, chest press, seated row, biceps curls and triceps extensions). The aerobic training for each period was prescribed based on training adherence (i.e. based on whether the patient followed the recommendations for the previous cycle) and

changes in aerobic capacity. The detailed training recommendations are presented in Table 1.

4. Data analysis

The outcomes are presented by absolute and relative changes throughout the measurement times. In order to compare changes induced in lactate and heart rate curves obtained during CPET, area under the curve (AUC) analyses were conducted. Data analyses were performed using Microsoft Excel® 2016 (Microsoft, Redmond, WA).

5. Findings

The anthropometrics of the patient throughout the intervention period are presented in Table 2.

5.1. Training adherence

The majority of training sessions was performed by running, while occasionally mountain biking and ski touring was carried out. Following the initial testing, the patient developed a tendinopathy in the left knee joint, which prevented him from carrying out the prescribed training until November 2017. Furthermore, the patient reported severe infections on July 4th to July 11th, 2018, October 29th to November 15th, 2018 and February 11th to February 24th, 2019. The total aerobic training performed is presented in Table 3. In addition to the aerobic training, during the final 4 months of the intervention the patient performed on average 1.3 ± 0.6 hypertrophic strength training sessions per week, corresponding to a training adherence of 65.0%.

5.2. Physical functioning and patient-reported outcomes

Initially, VO_2peak dropped from August 2017 to January 2018 from 50.9 $ml \cdot kg^{-1} \cdot min^{-1}$ to 45.6 $ml \cdot kg^{-1} \cdot min^{-1}$ (-10.4%). Thereafter, VO_2peak linearly increased until August 2018 (+16.0%) and further from February 2019 to the final measurements in June 2019 (from 52.1 $ml \cdot kg^{-1} \cdot min^{-1}$ to 55.4 $ml \cdot kg^{-1} \cdot min^{-1}$, +6.3%). The overall improvement of VO_2peak from August 2017 until June 2019 was +8.8%.

Blood lactate and HR kinetics throughout the CPET are presented in Fig. 1. AUC of heart rate and blood lactate was lower at the end of the intervention (- 9.9% and - 41.1%, respectively).

Table 1
Training recommendations provided to the patient.

Duration	Training recommendation
August 2017–January 2018	2–3 x per week LICT, 65–70% HR_{max}, 45 minutes per session
January 2018–May 2018	2–3 x per week LICT, 65–70% HR_{max}, 45 minutes per session
May 2018–August 2018	Week 1–4: 2 x per week LICT at 65–70% HR_{max}, 60 minutes 1 x per week HIIT, 4×4 minutes at 85% HR_{max} with 2 minutes rest at 70% of HR_{max} Week 5 onwards: 1 x per week LICT at 65–70% HR_{max}, 60 minutes 2 x per week HIIT, 4×4 minutes at 85% HR_{max} with 2 minutes rest at 65–70% of HR_{max}
August 2018–February 2019	1 x per week LICT at 65–70% HR_{max}, 60 minutes 2 x per week HIIT, 4×4 minutes at 85% HR_{max} with 2 minutes rest at 65–70% of HR_{max}
February 2019–June 2019	1 x per week LICT at 65–70% HR_{max}, 75 minutes 2 x per week HIIT, 4×4 minutes at 85% HR_{max} with 2 minutes rest at 65–70% of HR_{max} 1–2 x per week strength training, 3 x 12–15 RM

HR_{max}: maximal heart rate; LICT: Low-intensity continuous training; HIIT: High-intensity interval training; RM: repetition maximum; Strength training included the following exercises: leg press, leg extension, chest press, seated row, biceps curls and triceps extensions.

Following a short peak in January 2018, leg press strength linearly decreased from 175 kg to 160 kg until strength training was implemented in February 2019 (Fig. 2). Thereafter, an increase in maximal strength back to the baseline level of 170 kg was observed.

Lung function varied throughout the intervention (Fig. 3). However, a tendency for improvements was observed in VC, FVC and FEV_1 throughout all measurement times. Compared to baseline, VC, FVC and FEV_1 increased during the final measurements by 4.7%, 9.8%, and 9.3%, respectively.

Changes in the basic blood count are presented in Table 4. Fluctuations were observed throughout all measurement points, without indicating a positive or negative trend.

Changes in disease-specific QoL are presented in Fig. 4. Constant trends of improvement across all measurement times were only observed for "vitality", while no changes were found for "treatment burden". Changes in all other dimensions did not follow a linear pattern. Based on the documents provided, the patient was free of severe infections at the time of measurements.

6. Discussion

The aim of this case report was to assess the physical trainability of a patient diagnosed with PCD. To the best of our knowledge, this is the first evidence to show that regular low-intensity and vigorous training leads to improvements in aerobic capacity and muscle strength in a patient diagnosed with PCD. However, only minor changes in QoL were observed and the training did not systematically affect inflammatory markers based on the basic blood counts.

Cardiopulmonary fitness is traditionally considered as an important independent predictor of disease mortality [23]. In a recent meta-analysis on the associations of VO_2peak and mortality in CF, low levels of VO_2peak (i.e. < 45 $ml \cdot kg^{-1} \cdot min^{-1}$) were associated with a 4.9 fold higher risk of mortality [25]. These findings are important because in a previous cohort study with 44 children and young men diagnosed with PCD (median age 14.8 years), the relative median VO_2peak was only 37.9 $ml \cdot kg^{-1} \cdot min^{-1}$ [18]. While studies assessing VO_2peak as a prognostic marker specifically in PCD are still missing, improving aerobic fitness may likely be an important cornerstone in the management of PCD.

The patient included in our case report was initially assessed with a VO_2peak of 50.9 $ml \cdot kg^{-1} \cdot min^{-1}$. This finding is somewhat surprising, considering that previously VO_2peak was associated with FEV_1, especially indicating a FEV_1 below 85% of the predicted norm value to be indicative of very low aerobic fitness [18,24]. Indeed, FEV_1 in our patient fluctuated throughout the intervention, with a range from only 74.3% - 84.3% towards the end of the intervention. Similarly, also VO_2peak dropped during initial 3 months without training but increased thereafter throughout the remainder of the intervention, leading to an overall range from 45.6 $ml \cdot kg^{-1} \cdot min^{-1}$ in November 2017 to 55.4 $ml \cdot kg^{-1} \cdot min^{-1}$ in June 2019 (+21.5%). While the improvements in FEV_1 and VO_2peak were somewhat similar, we cannot confirm FEV_1 to be a direct indicator of aerobic capacity. However, prior to contacting us, the patient reported to perform regular mountain bike and ski tours, a large portion of it having been performed at altitude. In fact, previous studies suggested the low aerobic fitness to be associated with a sedentary lifestyle, caused by the burden of the disease [18,24]. Therefore, our findings are of high significance, showing that even avoiding sedentary behaviour will remarkably increase aerobic fitness in patients with PCD, without inducing notable adverse events. Moreover, already high degrees of aerobic capacity may be further enhanced by structured physical training and as such, the physical trainability of these patients appears to be similar to that of healthy peers.

The changes in VO_2peak appeared to be somewhat in line with the training adherence. For example, initially the patient did not adhere to the prescribed training due to an injury and consequently, VO_2peak initially dropped by about 10% and did not improve until the training

Table 2

Changes in body composition of the patient throughout the intervention.

	Aug 2017	Jan 2018	May 2018	Aug 2018	Feb 2019	June 2019	Δ% Pre - Post
Body mass [kg]	67.0	66.4	62.7	63.8	63.2	64.4	**- 3.9**
Body height [cm]	183.3	N/A	N/A	N/A	N/A	N/A	**N/A**
Body mass index [kg·m^{-2}]	19.9	19.6	18.6	18.8	18.7	19.1	**- 4.4**
Fat mass [kg]	6.0	7.0	6.2	5.6	5.9	7.0	**+ 16.7**
Fat mass [%]	9.0	10.5	9.8	8.8	9.3	10.9	**+ 1.8**
Lean mass [kg]	61.0	59.4	56.5	58.1	57.4	57.4	**- 5.9**
Lean mass [%]	91.0	89.5	90.2	91.2	90.8	89.1	**- 1.9**
Waist circumference [cm]	76.0	74.0	72.5	72.0	74.0	76.5	**+ 0.7**

Δ% refers to changes from August 2017 to June 2019; N/A: Not assessed.

Table 3

Aerobic training performed throughout the intervention period.

	Total number of sessions (mean ± SD)	Adherence (% of total training sessions prescribed)	Duration (hh:min:ss, mean ± SD)	Distance (km, mean ± SD)	Mean heart rate (bpm, mean ± SD)
August 2017 – November 2017	No training				
November 2017 – January 2018	1.8 ± 1.1	72.0%	00:57:10 ± 00:36:20	5.7 ± 1.3	149.1 ± 7.6
January 2018 – May 2018	2.3 ± 1.2	92.0%	01:26:10 ± 00:49:41	6.8 ± 3.7	140.4 ± 10.4
May 2018 – August 2018	2.6 ± 0.7	86.7%	00:52:55 ± 00:07:30	6.4 ± 0.4	134.9 ± 10.2
August 2018 – February 2019	1.8 ± 1.0	60.0%	01:12:12 ± 01:05:43	6.8 ± 2.4	135.9 ± 8.2
February 2019 – June 2019	3.0 ± 1.2	100.0%	01:08:53 ± 00:29:31	7.6 ± 3.2	150.9 ± 11.1

NB: Mean heart rate was recorded throughout each entire training session, including high- and low-intensity bouts.
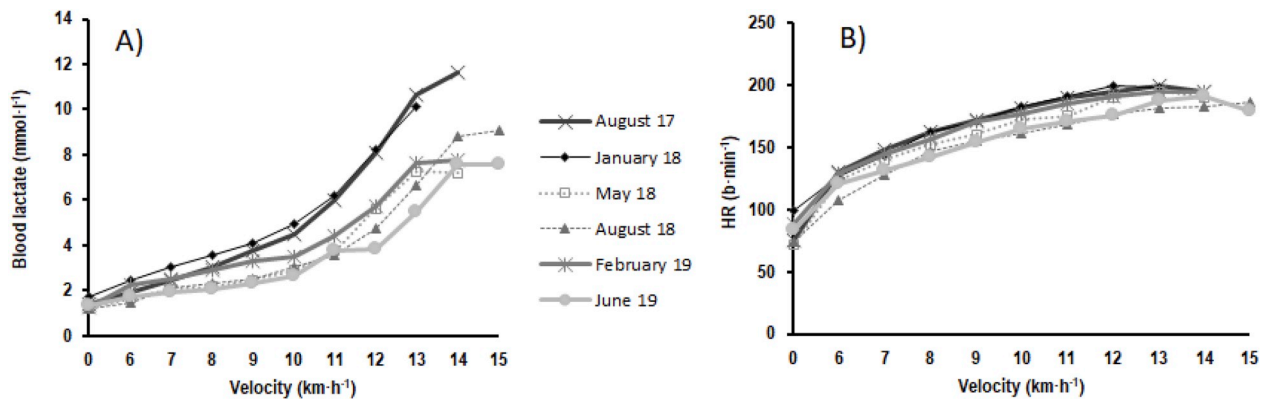

Fig. 1. Blood lactate (A) and heart rate kinetics throughout the CPET.
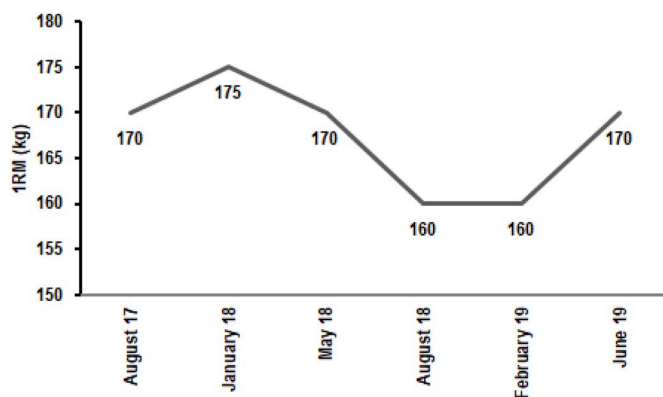

Fig. 2. Muscle strength of leg extensors throughout the intervention period.

volume was increased again (i.e. from November 2018 onwards). Similarly, the training adherence was rather low from August 2018 to February 2019 (i.e. 60%) and no changes in VO$_2$peak occurred during this period. However, it should be noted that a case report does not allow to conclude causalities and, thus, it cannot be ruled out that other factors such as biological variation have led to or contributed to the fluctuations in VO$_2$peak [1]. This is especially in light of the heterogeneity observed in PCD patients with regards to physical functioning [18,24]. Moreover, one should bear in mind that the susceptibility to respiratory tract infections is much higher in PCD patients compared to healthy controls [3, 14,17]. While severe infections were reported only during three 2-week periods throughout the entire intervention, especially NLR, PLR and SII indicated low-grade infections in the majority of measurement times [6]. Therefore, it is possible that we have not been able to assess absolute performance maxima throughout the performance tests.

Interestingly, in healthy subjects, chronic aerobic training typically leads to a downregulation of pro-inflammatory cytokine gene expression, such as IL-8 and IL-15 [15]. Although, cytokines were not assessed
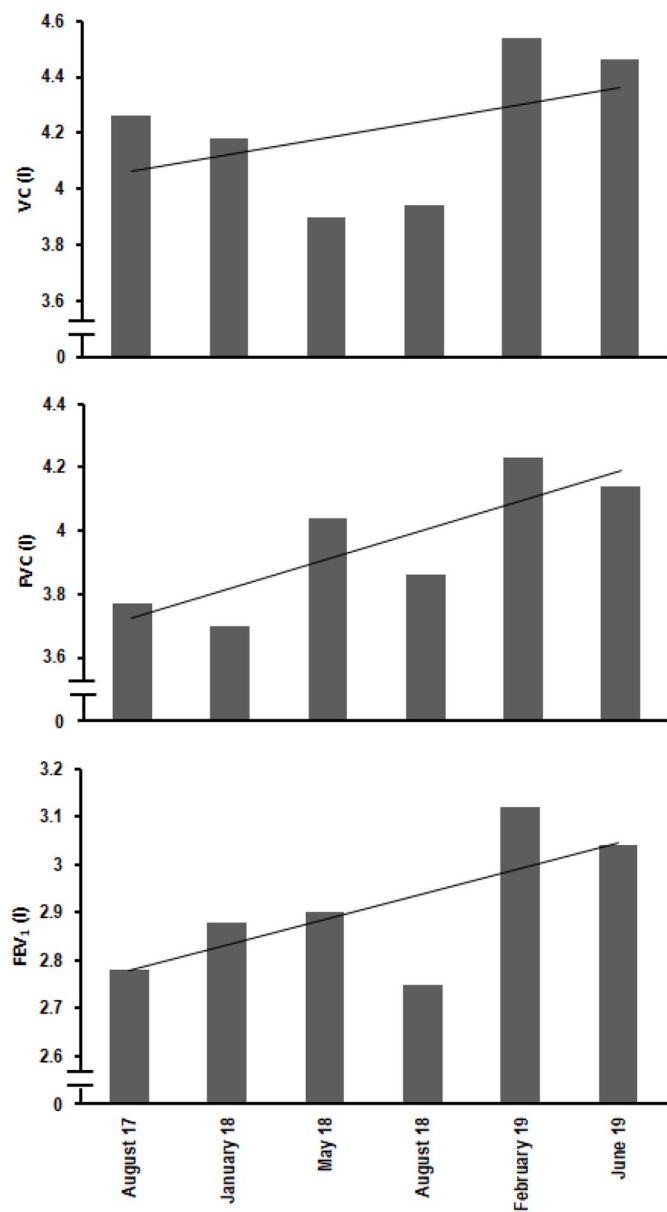
Fig. 3. Changes in A) vital capacity (VC), B) forced vital capacity (FVC) and C) forced expiratory volume in 1 second (FEV$_1$) throughout the intervention.

Table 4
Changes in the basic blood counts throughout the intervention.

	Aug 2017	Jan 2018	May 2018	Aug 2018	Feb 2019	June 2019
WBC [*10^3 μL]	4.7	6.5	5.1	6.3	6.8	5.3
RBC [*10^6 μL]	5.3	5.3	5.1	4.7	5.4	5.3
HGB [g · dl^{-1}]	15.5	15.6	14.8	14.0	15.4	16.6
HCT [%]	46.3	46.3	44.0	43.3	45.7	44.6
Lym [*10^3 μL]	1.6	1.5	1.6	1.4	1.7	1.6
Mxd [*10^3 μL]	0.9	0.6	0.6	0.9	0.5	0.4
Neut [*10^3 μL]	2.2	4.4	2.9	4.0	4.6	3.3
NLR	1.4	2.9	1.8	2.9	2.7	2.1
PLR	155.0	251.3	166.9	204.3	202.4	222.5
SII	341.0	1105.9	483.9	817.1	930.8	734.3

WBC: white blood cells; RBC: red blood cells; HGB: haemoglobin; HCT: haematocrit; Lym: lymphocytes; Mxd: mixed cell content; Neut: neutrophils; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic inflammation index.

in the present case study, the basic blood counts indicate that improved aerobic capacity was not associated with adaptations in inflammatory markers. In fact, a similar phenomenon was also observed for changes in QoL. Contrary to our findings, it was previously shown that physical fitness is associated with improved overall QoL [8] and already short periods of regular aerobic training (i.e. 12 weeks) may reduce scores for "treatment burden" and "emotional functioning" in PCD patients [20]. In the present study, we included a PCD-specific questionnaire, covering all main aspects of the disease [16]. Overall, the scores across all measurement times indicated a severe impairment of the patient's QoL, which was especially reflected in the domain of "treatment burden". This category covers the time-consuming aspects of disease management, including medication, physician appointments and respiratory therapy. In fact, regular physical training requires time as well and may be considered as an increased disease burden. This may also explain why in the present case no changes were observed in this domain. Moreover, we followed-up this patient over the course of nearly two years. Most previous studies including other respiratory diseases spanned over a much shorter duration only. Therefore, the heterogeneity of QoL scores

across the measurement times in our study also indicate the complexity of the disease, where seasonal aspects (e.g. humidity, pollen activity, temperature) seem to have a much larger effect on wellbeing than the physical training.

Interestingly, linear improvements of QoL were only observed in the domain "vitality" but not "physical functioning". While "vitality" mainly covers aspects related to tiredness and fatigue, "physical functioning" relates to fitness, including aerobic capacity and muscle strength. Initially, the main aim of the training prescription was to improve aerobic fitness. However, the aerobic running training led to a systematic reduction in muscle strength by 10-15 kg, as was previously shown in healthy recreational endurance athletes [21]. The lowest values of muscle strength were recorded from August 2018 to February 2019, and correspond well with the lowest score of "physical functioning". Based on the reduced muscle strength, we decided to include regular strength training for the remainder of the training period. Even though training adherence was rather low (i.e. 65%), significant increases in leg strength were observed and were again accompanied by higher scores in "physical functioning". Consequently, not only aerobic training but also structured strength training should be incorporated into the exercise regimen for a successful supportive therapy.

7. Conclusion

This case study provides first evidence for the effectiveness of regular structured physical training to improve aerobic fitness and muscle strength in patients with PCD. In fact, the observed improvements follow a dose-response relationship with the type of training and overall training adherence and indicate the trainability of these patients to be similar to that of healthy peers. However, our data further shows that changes in physical fitness may not ultimately be related to changes in QoL or inflammatory markers. Nevertheless, we provide reasoning to further stress the implementation of individualized physical training in the management of PCD, including both aerobic and strength exercises.

Declarations

Competing interests

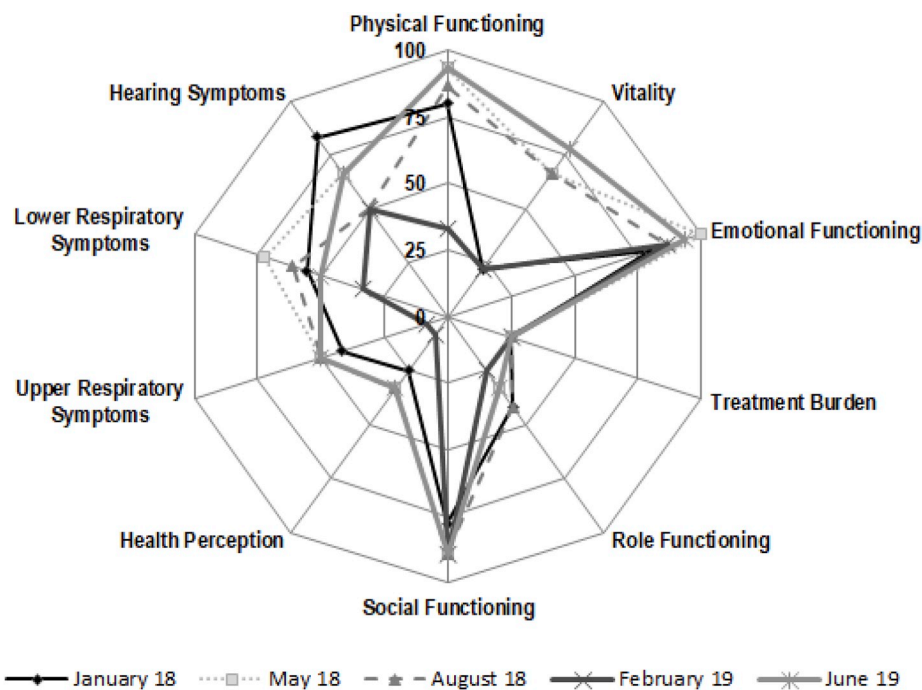The authors declare that they have no competing interests.

Fig. 4. Changes of disease-specific quality of life throughout the intervention. This questionnaire was implemented for the first time in January 2018.

Conflicts of interest

There are no conflicts of interest to declare. The study was self-funded by the institute.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100925.

References

[1] M. Bagger, P.H. Petersen, P.K. Pedersen, Biological variation in variables associated with exercise training, Int. J. Sports Med. 24 (6) (2003) 433–440, https://doi.org/10.1055/s-2003-41180. eng.

[2] G. Borg, Perceived exertion as an indicator of somatic stress, Scand. J. Rehabil. Med. 2 (2) (1970) 92–98 (eng).

[3] A. Bush, R. Chodhari, N. Collins, et al., Primary ciliary dyskinesia: current state of the art, Arch. Dis. Child. 92 (12) (2007) 1136–1140, https://doi.org/10.1136/adc.2006.096958. eng [Internet].

[4] A. Bush, P. Cole, M. Hariri, et al., Primary ciliary dyskinesia: diagnosis and standards of care, Eur. Respir. J. 12 (4) (1998) 982–988 (eng).

[5] M.E. Coren, M. Meeks, I. Morrison, R.M. Buchdahl, A. Bush, Primary ciliary dyskinesia: age at diagnosis and symptom history (Oslo, Norway: 1992), Acta Paediatr. 91 (6) (2002) 667–669 (eng).

[6] J. Fest, R. Ruiter, M.A. Ikram, T. Voortman, C.H.J. van Eijck, B.H. Stricker, Reference values for white blood-cell-based inflammatory markers in the Rotterdam study: a population-based prospective cohort study, Sci. Rep. 8 (1) (2018), 10566, https://doi.org/10.1038/s41598-018-28646-w. eng [Internet].

[7] Y. Geng, Y. Shao, D. Zhu, et al., Systemic immune-inflammation index predicts prognosis of patients With esophageal squamous cell carcinoma: a propensity

score-matched analysis, Sci. Rep. 6 (2016), 39482, https://doi.org/10.1038/srep39482. eng [Internet].

[8] H. Hebestreit, K. Schmid, S. Kieser, et al., Quality of life is associated with physical activity and fitness in cystic fibrosis, BMC Pulm. Med. 14 (2014) 26, https://doi.org/10.1186/1471-2466-14-26. eng [Internet].

[9] K. Jain, S.P.G. Padley, E.J. Goldstraw, et al., Primary ciliary dyskinesia in the paediatric population: range and severity of radiological findings in a cohort of patients receiving tertiary care, Clin. Radiol. 62 (10) (2007) 986–993, https://doi.org/10.1016/j.crad.2007.04.015. eng [Internet].

[10] B. Joschtel, S.R. Gomersall, S. Tweedy, H. Petsky, A.B. Chang, S.G. Trost, Effects of exercise training on physical and psychosocial health in children with chronic respiratory disease: a systematic review and meta-analysis, BMJ Open Sport. Exerc. Med. 4 (1) (2018), e000409, https://doi.org/10.1136/bmjsem-2018-000409. eng [Internet].

[11] M. Kartagener, Zur pathogenese der Bronchiektasien, Beiträge Klin. Tuberk. 83 (4) (1933) 489–501, https://doi.org/10.1007/BF02141468 [Internet].

[12] M.R. Knowles, L.A. Daniels, S.D. Davis, M.A. Zariwala, M.W. Leigh, Primary ciliary dyskinesia. Recent advances in diagnostics, genetics, and characterization of clinical disease, Am. J. Respir. Crit. Care Med. 188 (8) (2013) 913–922, https://doi.org/10.1164/rccm.201301-0059CI. eng [Internet].

[13] C.E. Kuehni, T. Frischer, M.-P.F. Strippoli, et al., Factors influencing age at diagnosis of primary ciliary dyskinesia in European children, Eur. Respir. J. 36 (6) (2010) 1248–1258, https://doi.org/10.1183/09031936.00001010. eng.

[14] M.W. Leigh, J.E. Pittman, J.L. Carson, et al., Clinical and genetic aspects of primary ciliary dyskinesia/Kartagener syndrome, Genet. Med. Off. J. Am. Coll. Med. Genet. 11 (7) (2009) 473–487, https://doi.org/10.1097/GIM.0b013e3181a53562. eng [Internet].

[15] D. Liu, R. Wang, A.R. Grant, et al., Immune adaptation to chronic intense exercise training: new microarray evidence, BMC genomics 18 (1) (2017) 29, https://doi.org/10.1186/s12864-016-3388-5. eng [Internet].

[16] J.S. Lucas, L. Behan, A. Dunn Galvin, et al., A quality-of-life measure for adults with primary ciliary dyskinesia: QOL-PCD, Eur. Respir. J. 46 (2) (2015) 375–383, https://doi.org/10.1183/09031936.00216214. eng [Internet].

[17] J.S. Lucas, A. Burgess, H.M. Mitchison, E. Moya, M. Williamson, C. Hogg, Diagnosis and management of primary ciliary dyskinesia, Arch. Dis. Child. 99 (9) (2014) 850–856, https://doi.org/10.1136/archdischild-2013-304831. eng [Internet].

[18] A. Madsen, K. Green, F. Buchvald, B. Hanel, K.G. Nielsen, Aerobic fitness in children and young adults with primary ciliary dyskinesia, PloS one 8 (8) (2013), e71409, https://doi.org/10.1371/journal.pone.0071409. eng [Internet].

[19] A.M. Ring, F.F. Buchvald, M.G. Holgersen, K. Green, K.G. Nielsen, Fitness and lung function in children with primary ciliary dyskinesia and cystic fibrosis, Respir. Med. 139 (2018) 79–85, https://doi.org/10.1016/j.rmed.2018.05.001. eng [Internet].

[20] A.M. Schmidt, U. Jacobsen, V. Bregnballe, et al., Exercise and quality of life in patients with cystic fibrosis: a 12-week intervention study, Physiother. Theory Pract. 27 (8) (2011) 548–556, https://doi.org/10.3109/09593985.2010.545102. eng [Internet].

[21] M. Schumann, P. Pelttari, K. Doma, L. Karavirta, K. Häkkinen, Neuromuscular adaptations to same-session combined endurance and strength training in

recreational endurance runners, Int. J. Sports Med. 37 (14) (2016) 1136–1143, https://doi.org/10.1055/s-0042-112592. eng.

[22] H.C. Selvadurai, C.J. Blimkie, N. Meyers, C.M. Mellis, P.J. Cooper, P.P. van Asperen, Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis, Pediatr. Pulmonol. 33 (3) (2002) 194–200 (eng).

[23] A. Solomon, K. Borodulin, T. Ngandu, M. Kivipelto, T. Laatikainen, J. Kulmala, Self-rated physical fitness and estimated maximal oxygen uptake in relation to all-cause and cause-specific mortality, Scand. J. Med. Sci. Sport. 28 (2) (2018) 532–540, https://doi.org/10.1111/sms.12924. eng [Internet].

[24] G. Valerio, F. Giallauria, S. Montella, et al., Cardiopulmonary assessment in primary ciliary dyskinesia, Eur. J. Clin. Investig. 42 (6) (2012) 617–622, https://doi.org/10.1111/j.1365-2362.2011.02626.x. eng [Internet].

[25] F.M. Vendrusculo, J.P. Heinzmann-Filho, J.S. da Silva, M. Perez Ruiz, M.V. F. Donadio, Peak oxygen uptake and mortality in cystic fibrosis: systematic review and meta-analysis, Respir. Care 64 (1) (2019) 91–98, https://doi.org/10.4187/respcare.06185. eng [Internet].

[26] N. Ward, K. Stiller, A.E. Holland, Exercise as a therapeutic intervention for people with cystic fibrosis, Expert Rev. Respir. Med. 13 (5) (2019) 449–458, https://doi.org/10.1080/17476348.2019.1598861. eng [Internet].

[27] W.-M. Yang, W.-H. Zhang, H.-Q. Ying, et al., Two new inflammatory markers associated with disease activity score-28 in patients with rheumatoid arthritis: albumin to fibrinogen ratio and C-reactive protein to albumin ratio, Int. Immunopharmacol. 62 (2018) 293–298, https://doi.org/10.1016/j.intimp.2018.07.007. eng [Internet].

[28] R. Zahorec, Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill, Bratisl. Lek. Listy 102 (1) (2001) 5–14 (eng).