Journal of Cystic Fibrosis 22 (2023) 344–351

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

Quantity and quality of airway clearance in children and young people with cystic fibrosis

Emma Raywood[a], Harriet Shannon[a], Nicole Filipow[a], Gizem Tanriver[a], Sanja Stanojevic[b], Kunal Kapoor[a], Helen Douglas[a,c], Rachel O'Connor[d], Nicky Murray[e], Bridget Black[a], Eleanor Main[a,*]

[a] Physiotherapy, UCL Great Ormond Street Institute of Child Health, London, UK
[b] Community Health and Epidemiology, Dalhousie University Halifax, Canada
[c] Paediatric Cystic Fibrosis Unit, Great Ormond Street Hospital for Children NHS Trust, London, UK
[d] Paediatric Cystic Fibrosis Centre, Royal London Hospital, Barts Health NHS Trust, London, UK
[e] Paediatric Cystic Fibrosis Unit, Royal Brompton and Harefield NHS Foundation Trust, London, UK

ARTICLE INFO

Article history:
Received 23 June 2022
Revised 27 August 2022
Accepted 19 September 2022
Available online 7 October 2022

Keywords:
Airway clearance techniques
Chest physiotherapy
Paediatric
Physiotherapy
Respiratory

ABSTRACT

Children and young people with CF (CYPwCF) get advice about using positive expiratory pressure (PEP) or oscillating PEP (OPEP) devices to clear sticky mucus from their lungs. However, little is known about the quantity (number of treatments, breaths, or sets) or quality (breath pressures and lengths) of these daily airway clearance techniques (ACTs) undertaken at home. This study used electronic pressure sensors to record real time breath-by-breath data from 145 CYPwCF (6–16y) during routine ACTs over 2 months. ACT quantity and quality were benchmarked against individual prescriptions and accepted recommendations for device use. In total 742,084 breaths from 9,081 treatments were recorded. Individual CYPwCF maintained consistent patterns of ACT quantity and quality over time. Overall, 60% of CYPwCF did at least half their prescribed treatments, while 27% did fewer than a quarter. About 77% of pre-teens did the right number of daily treatments compared with only 56% of teenagers. CYPwCF usually did the right number of breaths. ACT quality (recommended breath length and pressure) varied between participants and depended on device. Breath pressures, lengths and pressure-length relationships were significantly different between ACT devices. PEP devices encouraged longer breaths with lower pressures, while OPEP devices encouraged shorter breaths with higher pressures. More breaths per treatment were within advised ranges for both pressure and length using PEP (30–31%) than OPEP devices (1–3%). Objective measures of quantity and quality may help to optimise ACT device selection and support CYPwCF to do regular effective ACTs.

© 2022 The Authors. Published by Elsevier B.V. on behalf of European Cystic Fibrosis Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

1. Introduction

Approximately 52,000 people in Europe, including >10,800 people in the UK, have cystic fibrosis (CF) [1,2]. People with CF have thick respiratory mucus and are susceptible to repeated respiratory infections that can lead to irreversible lung damage and premature death. Treatments can take a median 2 hours to complete every day with physiotherapy, including airway clearance techniques (ACTs), being one of the most time consuming therapies [3].

ACTs aim to clear mucus from the lungs, slow progression of CF lung disease, and improve lung recruitment and gas exchange [4]. Methods include specific breathing techniques or positive expiratory pressure (PEP) ACT devices, which increase intrapulmonary pressure when people breathe out against resistance. Cycles of breaths with PEP at 10–20cmH_2O are thought to raise functional residual capacity (FRC) and improve airflow in obstructed small airways through collateral ventilation, preventing premature airway collapse and increasing air volume behind obstructions to aid mucus clearance, an expiratory flow bias ensures secretions are mobilised centrally [5]. Some devices generate a constant PEP, others produce airway oscillations (OPEP) thought to enhance mucus clearance with shear forces [5,6]. The UKCF Registry report found 49% of adults and 76% of children and young people with CF (CYP-

* Corresponding author: Prof. Eleanor Main, Physiotherapy, UCL GOS Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, UK.
E-mail address: e.main@ucl.ac.uk (E. Main).

https://doi.org/10.1016/j.jcf.2022.09.008
1569-1993/© 2022 The Authors. Published by Elsevier B.V. on behalf of European Cystic Fibrosis Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

wCF) aged under 18 years old used PEP or OPEP devices as their primary or secondary ACT [2]. However, there is evidence from small studies in adults and children that ACT breath profiles vary between PEP devices and individuals with CF, even during supervised sessions [7,8].

Although ACTs are perceived as important, they are considered the most burdensome CF daily treatment [3]. Many find CF treatments difficult, with 70% regularly missing some daily treatments, most commonly ACTs or nebulised therapies [3,9]. CF centres review and correct or modify techniques at clinic visits [10], but little is known about the quantity or quality of unsupervised ACTs carried out at home or the impact of adherence on clinical outcomes for CYPwCF. Studies investigating ACT adherence from self-report tend to overestimate adherence. One study found self-report overestimated high adherence to ACT by 31% compared to an electronic method [11].

As a first step towards evaluating impact of ACTs on clinical outcomes, this analysis aimed to evaluate data from real time remote monitoring of ACTs by CYPwCF over 2 months, benchmarked against personalised ACT prescriptions and general principles of ACT quantity and quality that commonly appear in international guidelines related to PEP or OPEP device prescriptions [10,12,13].

2. Methods

Details on methods and recruitment for Project Fizzyo have been published[14]. Ethical approval was granted by London-Brighton and Sussex NREC (18/LO/1038). Informed consent was obtained from the parents/guardians of participants. Project Fizzyo was a longitudinal interrupted time series design cohort study of physiotherapy for CYPwCF, which included real time remote monitoring of breath-by-breath ACT data over 16 months [14]. This enabled detailed analysis of the way that CYPwCF performed daily unsupervised PEP or OPEP airway clearance treatments at home.

The first two months of Project Fizzyo (data presented in this paper) constituted observational baseline data collection. Participants carried out their usual ACT routines as prescribed by their physiotherapist, prior to the implementation of interventions.

Quantity of ACTs was evaluated against personalised prescriptions of:

i *Treatment frequency*: number of treatments per day
ii *Breath number:* number of breaths per treatment
iii *Set number:* number of sets per treatment, each set incorporating a cluster of 8–15 breaths followed by a visible pause for huffing or coughing to clear secretions [13]

Quality of ACTs was evaluated against personalised prescriptions and general principles of expiratory breath pressure or length that appear in best practice guidelines, including:

iv *Expiratory breath pressure*: ACT device resistance should be appropriate to achieve breaths with a "stable mid-expiratory pressure of 10–20cmH_2O" [10]
v *Expired breath length:* expiration at tidal volume should be only slightly active (not prolonged or forced) [10]

Specific expiratory breath lengths for ACTs have not been published, because they depend on age. For the purposes of benchmarking breath length in this study, reference values for normal respiratory rate (non-CF control population [15]), were used to predict average breath length in each child aged 6–16y, assuming an inspiratory:expiratory tidal volume ratio of 1:1.5. Expected expired breath length was predicted using the equation 0.052*age+1.35. 'Slightly active' expired breaths were assumed to be equal to, or longer than, this value. The expected 'normal' expired breath length for the participants at recruitment ranged from 1.64 to 2.22 seconds, increasing by 0.05 seconds per year of age.

2.1. Participants

Eligible CYPwCF aged 6–16 years were recruited between September 2018 and July 2019. They had a confirmed diagnosis of CF and were under the care of a participating London paediatric CF centre (Great Ormond Street Hospital for children (GOSH), Royal London Hospital or Royal Brompton Hospital).

Recruited CYPwCF had been prescribed one of four ACT devices to be used at least once daily as part of their routine physiotherapy: (Acapella Choice® (Smiths Medical, USA), Aerobika® (Trudell Medical, Canada), AstraTech® PEP/RMT (Astra Tech, Sweden), Pari PEP^{TM} S (Pari Medical, Germany)). These represented the most commonly prescribed devices at the 3 centres, and were all compatible with the remote monitoring sensor [14]. Participants could be prescribed more than one ACT to be used interchangeably and/or used entrained nebulisers. CYPwCF were excluded if they/their parents did not provide informed consent, they had a clinically significant medical condition other than CF or had not been prescribed one of the sensor-compatible ACT devices. At recruitment, participants indicated their ACT prescription, which was confirmed by the physiotherapist report/clinical notes. Self-reported non-adherence to prescribed ACT did not preclude participation.

2.2. Remote monitoring

At recruitment, each participant received their own Project Fizzyo chipped electronic ACT sensor [14], and had training on its daily use. The sensor was connected to their regular ACT device and recorded pressure-time data during ACTs. After treatment, the sensor was synced manually via Bluetooth to a Fizzyo app but, if participants forgot, the chip memory could store at least a week of data. Synced pseudonymised data were stored and analysed in the secure GOSH digital research environment (DRE; goshdrive.com) Azure cloud.

2.3. Data processing and statistical methods

An ACT data processing pipeline, written in R [16], stabilised baseline drift and cleaned outliers in the raw pressure-time data before ACT features were labelled (supplementary material). Expired breath length and pressure values were averaged per treatment and per participant. Adherence to each child's personalised prescription and general ACT principles were calculated as a percentage per treatment and summarised per week and for the 2-month study duration. Adherence was defined as high (=>75% of prescribed), moderate (50% to <75%), low (25 to <50%), very low (>0 to <25%), or non-adherent (0%). All treatments >15 seconds with at least 3 breaths were counted even if the quality of breaths was poor (supplementary material). Adherence could be >100% if more than the prescribed number of treatments, breaths or sets were recorded.

Summary data were presented as mean (SD) or median (IQR). Between group comparisons of individuals used Chi-squared tests for categorical variables and Kruskal-Wallis, ANOVA or T-tests for numeric data, based on variable distribution. Spearman's correlation coefficients (CC) and linear regression defined relationships between variables. Statistical analyses were conducted using SPSS (IBM, Version 27.0) and R [16] within the GOSH DRE.

3. Results

In total, 145 CYPwCF (74 male, 71 female), aged 6–16years (mean (SD) 10.2y (2.9)), were recruited. The population represented a wide range of CF clinical phenotypes representative of the recruiting sites (Table 1). The data collection period consisted

Table 1
Participant demographics at recruitment.

n		145 (GOSH 75 (51%); RBH 40 (28%); RLH 30 (21%))
Age	years	10.2 (2.9)
Male: Female ratio		74:71
Height	cm	137.9 (16.6)
	z-score	−0.18 (0.89)
Weight	kg	34.3 (12.4)
	z-score	−0.06 (0.87)
BMI	kg/m^2	17.3 (2.7)
	z-score	0.08 (0.90)
Spirometry FEV_1	L	1.75 (0.59)
	%pred	88.3 (15.4)
	z-score	−0.97 (1.27)
FVC	L	2.17 (0.77)
	%pred	95.4 (13.4)
	z-score	−0.40 (1.14)
Genotype F508del:	heterozygous	79 (54%)
	homozygous	46 (32%)
	no copies	20 (14%)
Prescribed CFTR Modulators [a]		8 (6%)
Number of IV antibiotic courses in previous 12 months, including routine IV administration		1 (1.4)

Mean (SD) or n (%). Height, Weight and BMI z-scores from WHO 2006 [17], Spirometry predicted values from GLI 2012 [18]. GOSH: Great Ormond Street Hospital, RBH: Royal Brompton Hospital, RLH: Royal London Hospital.

[a] Baseline measures carried out from September 2018-July 2019 before modulator therapy was widely available in the UK. The current advice for patients on modulator therapies is to continue daily ACT treatments [3].

of a mean (SD) 62 (5) days per participant. Overall, 137 participants (94%) recorded at least one treatment with a median of 63 treatments/person (IQR 26 to 104). Eight participants (6%) did not submit any treatments and were classified as non-adherent; four reported technical difficulties, one confirmed total non-adherence to ACT, three gave no reason.

A total of 9081 treatments were recorded out of 16,270 prescribed treatments (56%). In addition, 742,084 of 1375,382 prescribed breaths (55%) were recorded. A minimum of 500 treatments were recorded from each of the four sensor compatible ACT devices.

3.1. ACT prescription

The most commonly prescribed ACT device differed at each site, most likely as a result of physiotherapist or patient preference or NHS procurement differences. Most participants (104, 72%), were prescribed only one ACT device, while 41 (28%) used 2–4 different ACTs interchangeably. Eighteen (12%) used two or more ACT devices that were compatible with the sensor and data were analysed as "multiple ACTs" (Table 2, footnote). Twenty-eight participants (19%) also used 1 or more ACTs not compatible with the sensor alongside their sensor compatible device (Table 2, footnote).

Most participants (116, 80%) were prescribed ACTs twice daily (Table 2). Three daily ACTs were prescribed for one participant, others were advised to increase from 2 to 3 daily treatments when symptomatic. Further, a range of personalised prescription protocols were observed (Table 2). The most popular were 100 breaths per treatment (10 sets of 10 breaths; 89 (61%) participants) and 200 breaths per day, (10 sets of 10 breaths twice daily; 71 (49%) participants). Manometers/pressure gauges were not used frequently, <2% of participants reported routine use.

3.2. Adherence to number of daily treatments

The average adherence to number of prescribed treatments was 62% (IQR 21 to 88%), but variable between participants (Table 2). Of those who were adherent (n = 137), adherence was high (=>75% of prescribed) in 55 CYPwCF (40%), moderate (50% to <75%) in 27 (20%), low (25 to <50%) in 18 (13%) or very low (>0 to <25%) in 37 (27%) CYPwCF respectively. Adherence to number of daily treatments was not significantly associated with age, sex, baseline FEV_1, number of prescribed treatments or breaths, type of ACT or use of a non-sensor compatible ACT (p values >0.05) but was significantly higher for pre-teen participants (<13y, 77%) compared with teenagers (13y+, 56%, p = 0.015).

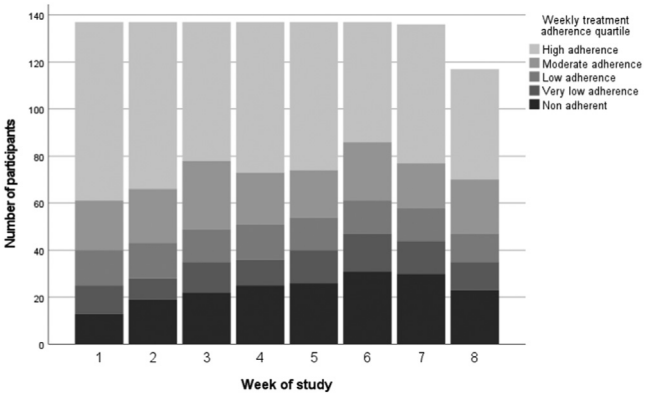

Fig. 1. Stacked bar chart of weekly treatment adherence quartile distribution. Non-adherent participants are not included (n = 8). The total number of participants was 137 in weeks 1–6, 136 in week 7 (1 participant withdrawal), 117 in week 8 (due to some participants moving to the next study stage).

Adherence was highest during the first two weeks of the study (79%), with over half of participants in the high adherence quartile. In subsequent weeks, the quartile distribution was relatively stable and appeared to be consistent amongst most individuals (Fig. 1; high adherence 37–47%, moderate 14–21%, very low and low 8–12%, non-adherent 16–23%).

3.3. Adherence to breath count

In general, CYPwCF had a habitual pattern to their ACTs and the number of breaths per treatment. A median (IQR) of 81 (56 to 105) breaths per treatment were recorded, with 99% (72% to 112%) adherence to number of prescribed breaths. In 98 CYPwCF (72%), breath number exceeded 75% of the prescription with 74 recording over 95% of prescribed breaths per treatment.

A third of treatments (31%) had a breath count less than 75% of prescription. Only 16 participants (12%) had low breath count (25 to <50% of prescribed) and 2 participants (1%) had very low breath

Table 2
Participant ACT prescriptions and adherence.

ACT Prescription	**Participants** n (%)	**Recruited age,** years mean (SD)	**Treatment adherence%** median (IQR)	**Breath count adherence%**
ACT devices compatible with the sensor				
Acapella OPEP	68 (47%)	9.44 (2.50)	52 (21 to 82)	93 (74 to 114)
Aerobika OPEP	26 (18%)	10.98 (3.16)	68 (21 to 89)	97 (74 to 105)
AstraTech PEP	8 (6%)	11.42 (3.42)	48 (25 to 92)	96 (72 to 110)
Pari PEP	25 (17%)	10.56 (2.82)	87 (20 to 93)	101 (66 to 109)
Multiple ACTs [a]	18 (13%)	10.91 (3.06)	63 (17 to 73)	106 (91 to 128)
Using additional non-sensor compatible ACT(s) [b]	28 (19%)	8.87 (2.35)	56 (20 to 94)	105 (85 to 112)
Treatment number: daily prescription				
Once Daily	28 (19%)	9.46 (2.75)	46 (16 to 76)	101 (79 to 120)
Twice Daily	116 (80%)	10.37 (2.88)	63 (21 to 89)	100 (72 to 112)
Breath number: treatment prescription				
<=40 breaths	<5 (3%)	8.93 (2.05)	38 (13 to 63)	108 (75 to 111)
41–60 breaths	26 (18%)	9.74 (2.94)	77 (33 to 88)	105 (87 to 121)
61–80 breaths	25 (17%)	10.93 (3.09)	59 (22 to 77)	101 (79 to 120)
81–100 breaths	90 (62%)	10.19 (2.80)	61 (19 to 89)	91 (71 to 109)
Breath number: daily prescription				
<=50 breaths	<5 (3%)	11.02 (2.33)	16 (7 to 41)	87 (81 to 109)
51–100 breaths	36 (22%)	9.90 (2.52)	56 (27 to 82)	105 (81 to 113)
101–150 breaths	23 (16%)	10.00 (3.36)	67 (28 to 85)	104 (79 to 129)
151–200 breaths	82 (57%)	10.35 (2.91)	63 (20 to 91)	91 (72 to 109)

Adherence definitions in supplementary material table s1.

[a] Participants used more than one sensor compatible ACT device. The specific ACT device used during each treatment was not manually recorded and devices could be used interchangeably. 7 were using both Acapella and Aerobika, 11 were using a PEP and an OPEP device.

[b] Adherence percentage is from sensor compatible devices used by participants who also used 1 or more additional non-sensor compatible techniques. Alternative ACTs were; 8 bubble PEP, 6 exercise, 5 trampolining, 4 autogenic drainage, 4 Flutter, 3 percussion, 2 high frequency chest wall oscillation.

count (<25% of prescribed breaths), both of whom also had low treatment adherence. Breath count adherence was not significantly associated with device used, daily treatment prescription, number of breaths prescribed per treatment or per day, age, sex or baseline FEV_1 ($p > 0.05$).

3.4. Adherence to set count

Clear gaps between sets of breaths were identified in 4402 (52%) of recorded treatments, with 2872 treatments having between 3 and 10 sets. Overall, 17% of treatments with sets had the prescribed set count (i.e., 100% adherence) and 49% had +/−20% of the prescribed set of breaths. It was not possible to establish whether gaps between sets were used for forced expiratory techniques or were simply pauses.

3.5. Expiratory breath profiles

Examples of commonly observed, but diverse, breath shapes generated by ACT devices are shown in Fig. 2. Expiratory breath profiles were heterogenous between participants and ACT devices but generally consistent within and between treatments by individual participants.

The median (IQR) mid-expiratory breath pressure of 17.9cmH_2O (13.4 to 24.5cmH_2O); was within the recommended 10–20cmH_2O (Table 3) but the range was wide and differed significantly by device (Fig. 3a). The median exceeded 20cmH_2O for Acapella (22.7cmH_2O), which was significantly higher than the other ACTs ($p<0.01$). Approximately two thirds of all breaths using non-oscillating PEP devices were between 10 and 20cmH_2O, contrasting with one quarter of breaths through Acapella.

Similarly, the per participant median (IQR) expired breath length was 1.52 s (1.10 to 2.13; Table 3) but varied by device and participant age (Fig. 3b). Older CYPwCF had longer expired breath lengths (linear regression slope: 0.166, 95%CI 0.111 to 0.221 $p<0.001$). For Acapella and Aerobika, median expired breath lengths were 1.14 and 1.47 s respectively, lower than the age-predicted tidal expiratory breath length for even the youngest participant (1.64 s; Fig. 3b, see supplementary material) and significantly shorter than for PEP devices (AstraTech, 1.85 s $p = 0.024$; Pari 2.36 $p<0.001$) or Multiple ACTs (1.68 s, $p = 0.052$). Around half of AstraTech PEP and three-quarters of Pari PEP recorded breaths were 'adherent' for breath length per treatment. Only a small proportion of breaths through the Acapella (6.1%) or Aerobika (14.5%) were longer than the average age-appropriate tidal volume expired breath.

Breath length was inversely correlated with mid-expiratory breath pressure (Spearman's CC −0.49, 95% CI −0.51 to −0.47, $p<0.001$); higher breath pressures were associated with shorter breath length and vice versa. The average breath pressure vs length relationship was significantly different between ACT devices (Kruskal Wallis $p<0.001$; Fig. 3a,b). The proportion of breaths within the advised ranges for both pressure and length were highest for PEP devices (30–31%) and very low for OPEP devices (1–3%; Table 3).

4. Discussion

This is the first study to provide objective evidence of adherence to ACT prescriptions undertaken by CYPwCF at home, in terms of both quantity (number of treatments, breaths, or sets) and quality (breath pressures and lengths). Overall adherence to quantity of daily ACT prescriptions was variable between CYPwCF, with the full spectrum between regular high adherence and regular non-adherence demonstrated in the data. Analysis of granular breath-by-breath data suggested that, overall, the quality of ACT treatments was poor and device specific in relation to published general principles of PEP and OPEP device usage.

Remote monitoring of ACT habitual behaviour is advantageous as it objectively records both quality and quantity of ACTs, with minimal additional effort or burden to the participant. This is an improvement on current practice where no treatments are objectively recorded and the majority of adherence data relies on subjective recall. Further, objective measures provided novel insights into the quality of ACT treatments by CYPwCF. Pressure-time breath profiles, mid-expiratory pressure and expired breath length

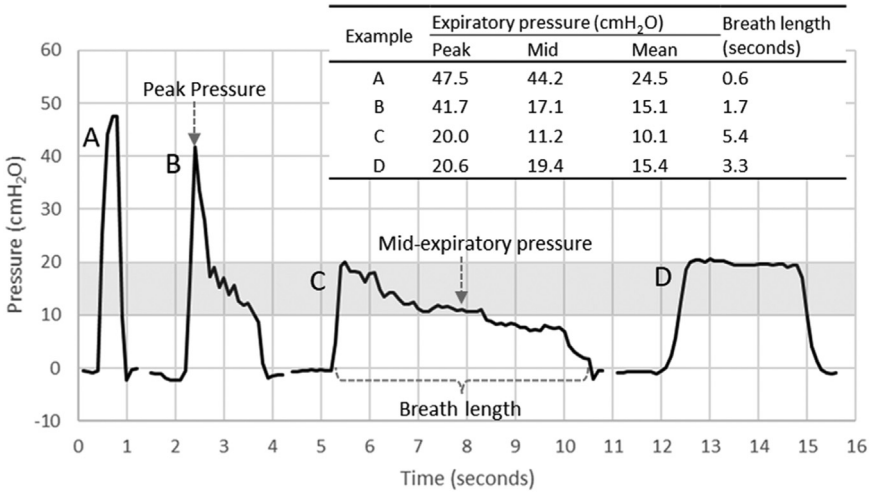

Fig. 2. Single breath examples of typical expiratory breath shape profiles recorded by the Fizzyo sensor for different devices (A&B: OPEP, C&D: PEP). There are clear differences in shape and pressure values of the breaths. The shaded area indicates the prescribed mid-expiratory pressure range 10–20cmH_2O, mid-expiratory pressure is measured as the pressure at 50% of the breath length.

Table 3
Expired breath pressure and breath length profiles and adherence.

		ACT (n participants)					Total (137)
		OPEP		PEP			
		Acapella (66)	**Aerobika (26)**	**AstraTech (7)**	**Pari (22)**	**Multiple ACTs (16)[a]**	
Expiratory breath pressure (cmH_2O)	Mid	22.7 (17.8 to 30.8)	16.1 (13.1 to 23.6)	15.0 (12.0 to 16.7)	13.8 (11.1 to 17.3)	12.8 (11.9 to 16.7)	17.9 (13.4 to 24.5)
	Peak	27.8 (22.7 to 38.3)	24.6 (18.3 to 30.5)	16.4 (13.9 to 20.4)	17.5 (14.7 to 21.7)	19.3 (15.4 to 24.5)	23.8 (17.8 to 32.7)
	Mean	15.5 (12.7 to 21.0)	12.3 (10.3 to 15.1)	12.8 (8.6 to 13.4)	12.3 (9.5 to 13.8)	10.2 (8.4 to 12.8)	13.1 (10.5 to 17.7)
Expiratory breath length (s)		1.14 (0.94 to 1.61)	1.47 (1.17 to 2.20)	1.85 (1.69 to 2.81)	2.36 (1.92 to 3.39)	1.68 (1.35 to 2.50)	1.52 (1.10 to 2.13)
Proportion of breaths adherent to guidelines (%)[b]	Pressure	25.5 (12.2 to 47.9)	55.8 (18.3 to 65.4)	68.7 (49.1 to 76.1)	65.0 (36.9 to 80.1)	53.5 (31.4 to 69.7)	42.0 (18.1 to 65.0)
	Length	6.1 (3.0 to 21.5)	14.5 (2.0 to 54.0)	50.6 (34.6 to 68.9)	72.2 (34.3 to 85.8)	20.6 (9.4 to 63.3)	15.1 (4.2 to 54.0)
	Both pressure and length	0.9 (0.2 to 4.1)	3.1 (0.7 to 23.3)	30.5 (13.2 to 45.9)	29.5 (12.9 to 65.4)	4.5 (1.0 to 13.0)	3.1 (0.5 to 15.5)
Total number of treatments		3638	1829	544	1974	1096	9081
Total number of breaths		283,423	141,903	38,637	176,853	101,268	742,084

Median (IQR) of per participant mean treatment values for breath profile parameters and adherence percentages by ACT device. ACT, airway clearance techniques, PEP positive expiratory pressure, OPEP oscillating positive expiratory pressure.

[a] Participant used more than one sensor compatible ACT. The specific ACT device being used during each treatment was not recorded.

[b] The percentage of adherent breaths of total breaths in a treatment. Adherence definitions in supplementary material. A breath with a mid-expiratory pressure of 10–20cmH_2O and/or with a length greater than an age related cut off was considered adherent.

were highly variable between individuals and significantly different between devices. In the future, expanding our approach to provide real time feedback regarding adherence and quality of ACT, based on objective measures of pressures and breath length, may help to improve adherence and optimise effectiveness for each CYPwCF.

Most participants were prescribed twice daily ACTs (80%) and asked to do 10 sets of 10 breaths per treatment (61%), the rest were prescribed a variety of other breath and set combinations. Objective measures indicated that 60% of CYPwCF were doing at least half of their prescribed treatments, while over one quarter of participants (27%) completed fewer than a quarter of prescribed treatments. The majority of pre-teenage CYPwCF (77%) did the right number of daily treatments compared with only 56% of teenagers.

Compared to previous studies that report adherence to ACT in CYPwCF based on self-report (patient diaries, questionnaires) or electronic monitoring of "Vest" usage, the mean treatment adherence (62%) and the percentage of low adherers (40%) were comparable [19–23]. Adherence to breath count was also generally good; once CYPwCF started a treatment, they tended to do the right number of breaths. Within guidelines, 8–15 breaths per set and/or treatments of 30 minutes, are commonly mentioned [10,13,24]. The '10 sets of 10′ prescription is not referenced but is likely a prescription that is easy to remember (for both staff and CYPwCF). Variations may be based on a physiotherapist's judgement of what the child or family are likely to tolerate. In the future, objective measures of adherence may provide an opportunity for CF centres to identify and support individual CYPwCF who have difficulties.

In terms of treatment quality, there is a general discordance between the advice given for use of ACT devices and what has been recorded and reported in the literature to date. Advice on breath profiles (pressure, length etc.) is typically based on generally accepted physiological principles of airway clearance, including interdependence, Pendelluft flow, collateral ventilation, equal pressure points two-phase gas-liquid flow mechanisms, and inspiratory/expiratory flow ratio [5,24]. These relate to the 'quality' domains of ACTs rather than 'quantity' domains. CYPwCF have some control over the 'quantity' of daily ACTs (number of treatments, breaths and sets), simply by counting. However, the 'quality' domains of ACTs appear to be heavily influenced by inherent properties of each device, rather than the age, sex or disease severity of the user. As a result, without objective measures of quality, many CYPwCF perceive they are adherent to their prescription whereas

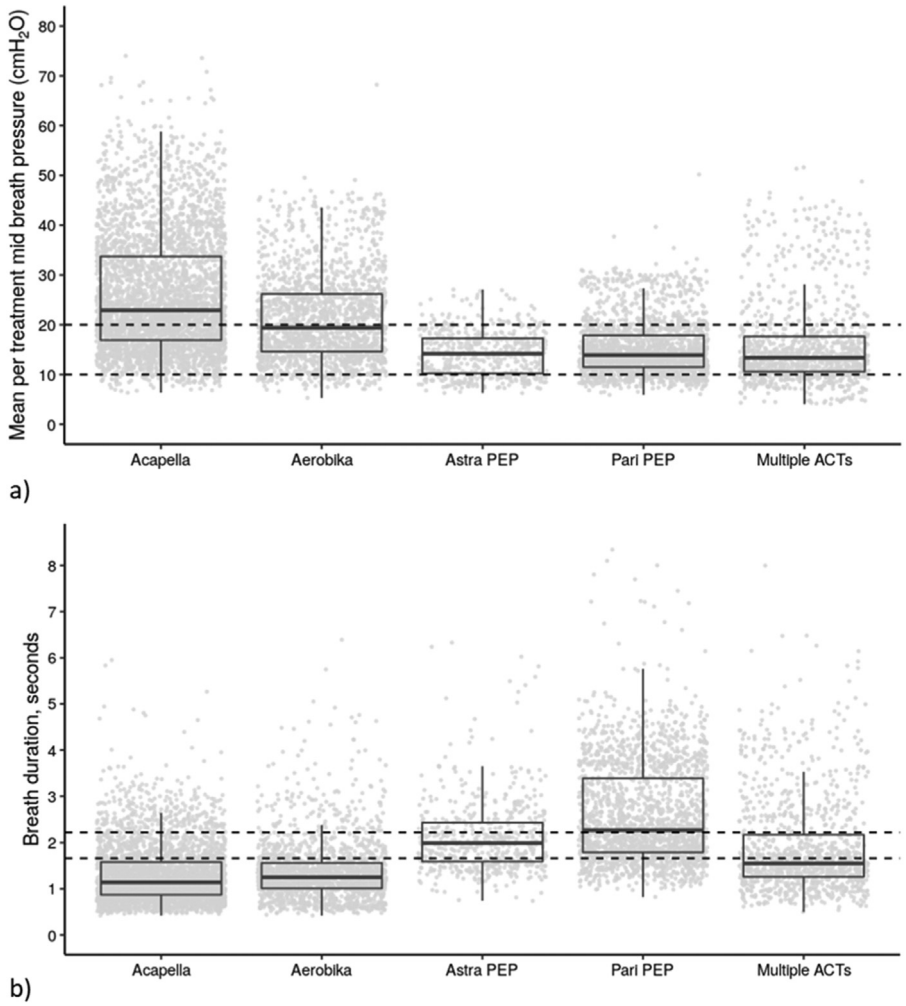

Fig. 3. Box plots of 9081 mean treatment values against ACT device type **a)** mid-expiratory breath pressure **b)** expiratory breath length. Each treatment mean value indicated by a grey dot, box showing median and IQR of all treatments for all participants. Dashed lines indicate a) 10 and 20cmH_2O (between these lines is the prescribed range), b) breath length age related threshold for the youngest (lower) and oldest (upper) participants at recruitment (below the lower line is shorter, and above the upper line is longer, than any participant's predicted minimum tidal breath length, see supplementary material).

the quality of their treatments may be outside what is considered physiologically beneficial.

Although some CYPwCF managed to produce 'good quality' breaths irrespective of the device they used, it was clear that some devices were far more likely to facilitate routinely 'good quality' breaths than others. In benchmarking the quality of breaths against the general principles of ACT advice, PEP devices performed better than OPEP devices. Overall, a small proportion of breaths were within recommended ranges for pressure and length combined, ~30% for PEP and 1–3% for OPEP devices. PEP devices with higher inherent resistance encouraged breaths that were longer with lower breath pressure (more likely to meet recommendations). Devices with lower internal resistance (e.g. Acapella) encouraged breaths of high pressure and shorter length, often without stable or sustained mid-expiratory pressure. Device specific breath profiles are especially important in younger CYPwCF, who may not yet have the degree of understanding or coordination to appropriately control their breathing during ACTs. Further work is needed to understand how the quality of habitual ACT impacts clinical outcomes in CYPwCF.

Two previous studies recorded ACT breath profiles with a flow or pressure sensor; both included fewer participants for shorter durations. The first study included 209 Aerobika breaths from 21 CYPwCF aged 5–17y [8] and also found breath profiles varied significantly between CYPwCF even during supervised treatments with consistent training by one physiotherapist. OPEP tended to be performed poorly by CYPwCF, with breaths rarely meeting recommendations. Peak breath pressures much higher than advised (>78cmH_2O) and time-pressure traces like those recorded by the Fizzyo sensor were also observed. More forceful shorter breaths were most common in pre-teen participants. A second study with a 'PEPtrac' electronic sensor in 18 adults with CF [7] recorded 110 (supervised and unsupervised) ACT treatments from Acapella, Aerobika or Pari PEP. It also identified significant differences in breath profiles by device, including significantly longer breaths with Pari PEP than the OPEP devices. This suggests the observed ACT patterns by device in our study persist into adulthood and may be related to inherent device characteristics, with a fixed resistance supporting sustained exhalation that oscillation does not. This supports our hypothesis that predominant 'device generated' pressure-time breath profiles and mid-expiratory breath pressures are largely to do with the properties of each device, rather than the user.

There are limitations to the current study. Missing data did not necessarily indicate that ACT treatments were not undertaken, rather that data were not transmitted to the study team. CYP-

wCF may have used a device-independent ACT (e.g. trampolining), or carried out ACTs without the Fizzyo sensor in place. The specific ACT device and if entrained nebulisers were used was not recorded, entrained nebulisers may themselves have affected treatment duration and adherence. There were also some issues reported with the sensor or app (3 damaged sensors required replacement) resulting in some ACT treatments being undertaken but not recorded. Nonetheless, the ACT data collected were larger than any other study worldwide to date and suggested clear habitual patterns of adherence for individual CYPwCF. Socioeconomic status and health literacy, both known to influence adherence, were not available in registry. Further, these data were collected before wide availability of highly effective modulator therapies in the UK so the effect of modulator therapies on adherence could not be established.

5. Conclusions

Analysis of ~750,000 breaths from over 9000 ACT treatments by 137 CYPwCF provided a unique insight into the way that ACTs are undertaken at home, and the extent to which general principles of using ACT devices are adhered to by CYPwCF. Treatments were usually of the prescribed number of breaths, although quantity of ACTs varied between participants. The breath pressure and length (ACT quality) varied between participants and devices, which may impact on the effectiveness of ACTs. Objective measures of quantity and quality may help both physiotherapists and CYPwCF to choose appropriate ACT devices and ensure the treatments they are undertaking are optimised for secretion clearance.

Funding

Project Fizzyo was supported by the UCL Rosetrees Stoneygate prize (M712), a Cystic Fibrosis Trust Clinical Excellence and Innovation Award (CEA010), A UCL Partners award and the HEFCE Higher Education Innovation Fund (KEI2017–01–04). HD was funded by the CF Trust Youth Activity Unlimited SRC and an NIHR GOSH BRC internship. All work at UCL GOSICH is supported by the NIHR GOSH BRC. The views expressed are those of the authors and not necessarily those of the NHS, NIHR or Department of Health. The study is sponsored by UCL. The funders and sponsor played no role in the design of the study.

Conflict of interest statement

All authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Emma Raywood: Methodology, Formal analysis, Investigation, Writing – original draft, Visualization, Project administration. **Harriet Shannon:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Nicole Filipow:** Software, Formal analysis, Data curation, Writing – review & editing. **Gizem Tanriver:** Software, Formal analysis, Data curation. **Sanja Stanojevic:** Formal analysis, Writing – review & editing. **Kunal Kapoor:** Software, Validation, Formal analysis, Data curation, Writing – review & editing. **Helen Douglas:** Conceptualization, Methodology, Investigation, Writing – review & editing, Project administration. **Rachel O'Connor:** Investigation, Writing – review & editing. **Nicky Murray:** Investigation, Writing – review & editing. **Bridget Black:** Formal analysis, Writing – review & editing. **Eleanor Main:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision, Funding acquisition.

Acknowledgements

Thank you to the children and young people and their families who participated in this research. Also thank you to the paediatric CF teams at the Great Ormond Street, Royal Brompton and Royal London Hospitals. To Microsoft UK especially Greg Saul and Lee Stott who helped develop the Project Fizzyo app, sensor (with Ryan White, Michael Woollard and Alan Bannon) and data collection cloud storage infrastructure (with Tim Kuzhagaliyev). The Microsoft CSE team (including Olga Liakhovich, Tempest Van Schaik, Bianca Furtuna, Josh Lane, Pete Roden, Stephanie Marker, Christian Robles, Kristjana Popovski, Hannah Kennedy and Kristin Ottofy) who helped develop the ACT data cleaning and processing pipeline. The GOSH DRE team, Dean Mohamedally and UCL computer science students and physiotherapy MSc students.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.09.008.

References

[1] Orenti A., Zolin A., van Rens J., et al. ECFSPR Annual Report 2020. 2022.
[2] Shaikh N., Lee A.C .S, Cosgriff R., et al. UK cystic fibrosis registry annual data report 2020 - cystic fibrosis trust. 2022. Contract No.: version 4.
[3] Davies G, Rowbotham NJ, Smith S, et al. Characterising burden of treatment in cystic fibrosis to identify priority areas for clinical trials. J Cyst Fibros 2020;19(3):499–502.
[4] van der Schans C, Prasad A, Main E. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. Cochrane Database Syst Rev 2000(2):001401 CD.
[5] McIlwaine M, Button B, Nevitt SJ. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. Cochrane Database Syst Rev 2019(11).
[6] Morrison L, Innes S. Oscillating devices for airway clearance in people with cystic fibrosis. Cochrane Database Syst Rev 2017;5(5):CD006842.
[7] Ward N, Ward B, Stiller K, et al. Development of a device to measure adherence and pressure characteristics of positive expiratory pressure therapies used by adults with cystic fibrosis. Physiother Theory Pract 2020:1–9.
[8] O'Sullivan KJ, Collins L, McGrath D, et al. Oscillating Positive Expiratory Pressure Therapy May Be Performed Poorly by Children With Cystic Fibrosis. Respir Care 2019;64(4):398–405.
[9] Narayanan S, Mainz JG, Gala S, et al. Adherence to therapies in cystic fibrosis: a targeted literature review. Expert Rev Respir Med 2017;11(2):129–45.
[10] Morrison L, Parrott H. Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis, Fourth edition Association of Chartered Physiotherapists in Cystic Fibrosis. Cystic Fibrosis Trust 2020.
[11] Oates GR, Stepanikova I, Rowe SM, et al. Objective versus self-reported adherence to airway clearance therapy in cystic fibrosis. Respir Care 2019;64(2):176–81.
[12] Button BM, Wilson C, Dentice R, et al. Physiotherapy for cystic fibrosis in Australia and New Zealand: a clinical practice guideline. Respirology 2016;21(4):656–67.
[13] IPG/CF The blue book – 'Physiotherapy treatment for people with cystic fibrosis: from infant to adult'. 7th ed. International Physiotherapy Group for Cystic Fibrosis; 2019.
[14] Raywood E, Douglas H, Kapoor K, et al. Protocol for Project Fizzyo, an analytic longitudinal observational cohort study of physiotherapy for children and young people with cystic fibrosis, with interrupted time-series design. BMJ Open 2020;10(10):e039587.
[15] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011;377(9770):1011–18.
[16] R Core Team R: a language and environment for statistical computing computer program, version 3.5. 0. R Foundation for Statistical Computing; 2018.
[17] WHO. Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl 2006;450:76–85.
[18] Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40(6):1324–43.
[19] Modi AC, Cassedy AE, Quittner AL, et al. Trajectories of adherence to airway clearance therapy for patients with cystic fibrosis. J Pediatr Psychol 2010;35(9):1028–37.
[20] Oates GR, Stepanikova I, Gamble S, et al. Adherence to airway clearance therapy in pediatric cystic fibrosis: socioeconomic factors and respiratory outcomes. Pediatr Pulmonol 2015;50(12):1244–52.
[21] Mikesell CL, Kempainen RR, Laguna TA, et al. Objective measurement of adherence to out-patient airway clearance therapy by high-frequency chest wall compression in cystic fibrosis. Respir Care 2017;62(7):920–7.

[22] Goodfellow NA, Hawwa AF, Reid AJ, et al. Adherence to treatment in children and adolescents with cystic fibrosis: a cross-sectional, multi-method study investigating the influence of beliefs about treatment and parental depressive symptoms. BMC Pulm Med 2015;15:43.
[23] Flores JS, Teixeira F, Rovedder PM, et al. Adherence to airway clearance therapies by adult cystic fibrosis patients. Respir Care 2013;58(2):279–85.
[24] McIlwaine M, Bradley J, Elborn JS, et al. Personalising airway clearance in chronic lung disease. Eur Respir Rev 2017;26(143):160086.