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Measuring the effect of elexacaftor/tezacaftor/ivacaftor combination therapy on the respiratory pump in people with CF using dynamic chest radiography ☆

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ABSTRACT

Background: The CFTR modulator elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) leads to significant improvement in the symptoms and spirometry of people with cystic fibrosis (pwCF), but little evidence exists to understand its effect on respiratory pump function. Dynamic chest radiography (DCR) is a novel cineradiographic tool that identifies and tracks the chest wall and diaphragm throughout the breathing cycle, alongside fluoroscopic images of the chest of diagnostic quality.

Methods: In this observational work, we examined the spirometry and DCR of 24 pwCF before and after starting ELX/TEZ/IVA. DCR automatically tracked the hemidiaphragm midpoints and projected lung area (PLA) during tidal and deep breathing manoeuvres.

Results: ppFEV$_1$ (61±18 to 73±22, P<0.001) and ppFVC (77±16 to 88±15, P<0.001) improved significantly. DCR demonstrated a significant increase in hemidiaphragm excursion on both the right (18±11 to 26±9 mm, P<0.001) and left (21±11 to 31±11 mm, P<0.001) sides, as well as maximum hemidiaphragm speed during inspiration (right 22±14 to 31±11 mm/s, P=0.03; left 28±11 to 37±16 mm/s, P=0.02). PLA at end-expiration was significantly reduced (334±71 to 290±72cm^2, P<0.001), with a significant increase in ΔPLA (83±40 to 117±36cm^2, P<0.001).

Conclusions: DCR demonstrated significant improvements in hemidiaphragm excursion and ΔPLA in pwCF started on ELX/TEZ/IVA. These changes likely reflect a reduction in air trapping and improved elastic recoil of the chest, and are consistent with improvements seen in spirometry. The changes seen with DCR are physiologically plausible and correlate well with spirometry. DCR warrants further investigation as a tool for assessing the impact of CFTR-modulating therapies.

1. Introduction

The triple combination cystic fibrosis transmembrane conductance regulator (CFTR) modulator elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) (Vertex Pharmaceuticals, Inc., Boston, MA, USA) has been licensed in the United Kingdom (UK) for people with CF (pwCF) with a wide range of CFTR mutations since September 2020, and is now available to more than 95% of pwCF over the age of 12 years. Whilst other CFTR modulating drugs such as tezacaftor/ivacaftor (TEZ/IVA) may lead to a reduction in exacerbation rate and small increases in lung function, [1,2] the impact

Abbreviation: ANOVA, One-way analysis of variance; BMI, Body mass index; CF, Cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire-Revised; CFTR, Cystic fibrosis transmembrane conductance regulator; DCR, Dynamic chest radiography; ELX/TEZ/IVA, Elexacaftor/tezacaftor/ivacaftor; EU, European Union; FEV1, Forced expiratory volume of air in 1 second; FVC, Forced vital capacity; pwCF, People with cystic fibrosis; PLA, Projected lung area; pp, Percent predicted; SD, Standard deviation; TEZ/IVA, Tezacaftor/ivacaftor; UK, United Kingdom; US, United States [of America]; ΔPLA, Change in projected lung area.

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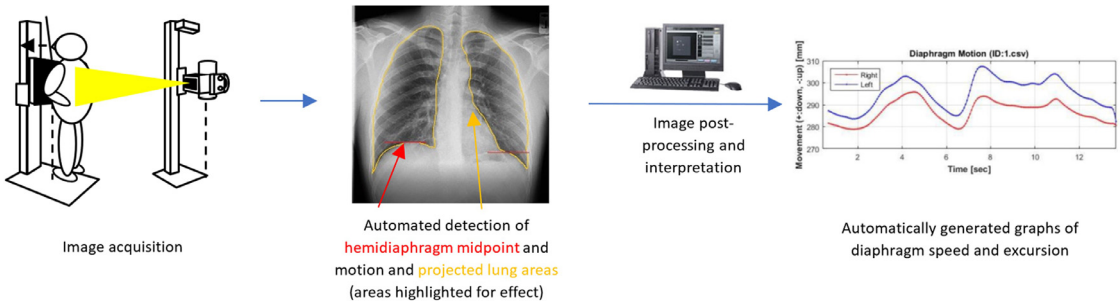

Fig. 1. Diagram of DCR workflow.

of ELX/TEZ/IVA is far more profound: in pwCF with FEV_1 40–90% predicted, it leads to a significant improvement in FEV_1, reduction in CF pulmonary exacerbation rate, improvement in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score, and improvement in body mass index (BMI) [3,4]. However, few studies have examined its effect on respiratory physiology. Its impact on chest wall dynamics and respiratory muscle function is less clear; murine models have shown that defective CFTR expressed in skeletal muscle causes muscle wasting and respiratory pump failure [5]. CFTR modulators improve body mass and reduce systemic inflammation. Both of these factors may positively impact inspiratory muscle strength, which is known to be negatively affected by loss of fat-free mass [6]. There is a need to develop sensitive methods to study the impact of CFTR modulators on lung health in pwCF, [7] particularly in detecting early or subtle changes in lung function [8,9].

Dynamic chest radiography (DCR), a novel, real time cineradiographic imaging system has recently become available for clinical use. DCR allows the identification and tracking of chest wall [10] and diaphragm motion [11,12] throughout the breathing cycle, alongside fluoroscopic images of the chest in the posteroanterior (PA) or lateral planes. DYNAMIC-CF is an ongoing single centre observational study that aims to validate the use of DCR in the assessment of lung health of pwCF at stable annual intervals as well as during pulmonary exacerbations [13]. Enrolment has been ongoing since December 2019 and included the time period during which ELX/TEZ/IVA was licensed for use in the UK. A number of previously enroled subjects had their annual DCR assessments performed both before and after starting ELX/TEZ/IVA, thus affording us with a unique opportunity to assess the effect of ELX/TEZ/IVA on thoracic cage dynamics and respiratory pump function.

2. Methods

Electronic hospital records of individuals enroled in DYNAMIC-CF (Haydock Research Ethics committee, 266778) were reviewed and those who had undergone DCR both before and after initiation of ELX/TEZ/IVA were identified. Individuals whose FEV_1 at the time of pre-ELX/TEZ/IVA DCR was significantly different ($\pm$>10%) from their yearly average were excluded, as were those enroled in the exacerbation sub-study arm of DYNAMIC-CF. The following were excluded: those who underwent DCR less than 28 days after commencing ELX/TEZ/IVA (in order to avoid inclusion of pwCF undergoing 'purge' symptoms); those who had a pulmonary exacerbation at the time of their repeat DCR; and those who discontinued ELZ/TEZ/IVA prior to their repeat DCR.

2.1. Imaging protocol

Posteroanterior (PA) DCR images were captured in the standing position over 10 seconds at 15 frames per second (fps), using a CMP 200DR 50 kW generator (CPI Inc., Palo Alto, CA, USA), AeroDR HD 17 × 17 flat panel detector (Konica Minolta, Inc., Tokyo, Japan), Varian Rad-60 Saphire X-ray tube, and Optica 60 collimator (Varian Medical Systems Plc, Palo Alto, CA, USA). The system is Conformité Européenne (CE) marked for cineradiographic imaging in the UK, EU and US. After coaching the patient briefly, images were acquired during the following respiratory manoeuvres:

1 tidal breathing
2 a deep breath to full inspiration
3 breathing out to full expiration

An example DCR image is available as an **online supplement**.

The points of maximum inspiration and full expiration were calculated by the DCR software, by determining the frames of minimum and maximum averaged pixel density respectively (for example at full inspiration, the lungs are expanded, hence less dense; the average pixel density of the entire image is therefore lowest). Projected lung area (PLA), the visible area of the lung in the PA plane, was calculated automatically at these points. Movement of the identified horizontal midpoint of each hemidiaphragm was measured by proprietary motion-tracking software (Konica Minolta, Inc., Tokyo, Japan).

All images were reviewed by a respiratory physician (TSF), single-blinded to the results, and corrected for motion-tracking calculation errors if appropriate. See Fig. 1 for a graphical representation of the image acquisition workflow. A full description of the DCR system can be found in the **online supplement**.

2.2. Pulmonary function testing

Spirometry was performed with a Spirostik™ spirometer (Geratherm, Bad Kissingen, Germany), or an Air Next handheld spirometer (NuvoAir AB, Stockholm, Sweden), both overseen by an Association for Respiratory Technology & Physiology (ARTP)-registered pulmonary physiologist to American Thoracic Society/European Respiratory Society (ATS-ERS) criteria. Forced expiratory volume of air in 1 second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio were recorded, along with percentage predicted values. BMI was recorded at the time of spirometry. DCR and spirometry were acquired within 48 hours of each other.

2.3. Statistical analysis

Statistical analysis was carried out using Rstudio (Boston, MA, USA) for R v4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided P-values of less than 0.05 were considered significant. Descriptive, normally distributed statistics are reported as mean $\pm$ standard deviation (SD). P-values were corrected for multiple comparisons using the Benjamini-Hochberg method. Normally distributed, paired data are reported using the paired Student's T-test, and unpaired data using the unpaired T-test. Comparison of single variables between multiple unpaired groups was made using one-way analysis of variance (ANOVA). Correlation was assessed

Table 1
demographic and anthropometric characteristics of subjects.

Characteristic	Number (%)	
Female	13 (54)	
P. aeruginosa chronic colonisation	23 (96)	
CF-related diabetes	15 (63)	
F508del/F508del	14 (58)	
F508del/minimal function	9 (38)	
F508del/none	1 (4)	
	Pre	**Post**
Age (years)	27±6	28±6
Height (cm)	167±10	167±10
Weight (kg)	64±11	70±4
BMI (kg/m^2)	23±3	25±4

using Spearman's rank correlation coefficient and reported using Spearman's rho and P-values. No power calculation was carried out in this observational work, due to the small sample size and lack of external normal reference values for the novel metrics produced by DCR.

3. Results

Of the 154 participants in the DYNAMIC-CF study, 20 were excluded as they were experiencing a pulmonary exacerbation at the time of DCR; 110 did not have DCR both before and at least 28 days after DCR, due to the constraints placed on the CF service due to the COVID-19 pandemic (see recruitment flowchart **supplement**). Twenty-four individuals (13 female) fulfilling the inclusion criteria were identified (Table 1). Seven were taking TEZ/IVA prior to their first DCR and a further seven subsequently commenced it before switching to ELX/TEZ/IVA prior to their second DCR: ten were naive to CFTR modulator therapy at the time of starting ELX/TEZ/IVA. The mean interval between the first DCR and commencement of ELX/TEZ/IVA was 270±205 days, with the mean interval post-commencement 189±102 days. All DCR images were of good quality, although in seven individuals an incomplete tidal breath precluded full tidal breathing analysis.

Table 2.

After starting ELX/TEZ/IVA, there was a significant improvement in ppFEV$_1$ ([mean±SD] 61±18 to 73±22%, P<0.001), ppFVC (77±16 to 88±15%, P<0.001), FEV$_1$/FVC (67±14 to 71±14, P=0.007) and BMI (23±3 to 25±4kg/m^2, P<0.001). DCR demonstrated a significant increase in the deep breathing excursion of both the right (18±11 to 26±9 mm, P<0.001) and left (21±11 to 31±11 mm, P<0.001) hemidiaphragms, as well as the maximum speed during inspiration (right 22±14 to 31±11 mm/s, P=0.03; left 28±11 to 37±16 mm/s, P=0.02). Peak speed during expiration following a deep breath increased significantly on the right (18±7 to 23±9 mm/s, P=0.02), and though increased on the left, was not significant (21±10 to 31±19 mm/s, P=0.08). Although the resting position of the hemidiaphragms at end-expiration was higher bilaterally, it only reached significance on the left (right 262±32 to 247±32, P=0.08; left 268±33 to 254±29 mm, P=0.01) (Fig. 2). There was no significant change in tidal breathing hemidiaphragm excursion or peak tidal breathing speeds.

PLA at maximum inspiration was not significantly different after initiation of ELX/TEZ/IVA (417±81 to 416±75cm^2, P=0.87), but PLA at end-expiration was significantly reduced (334±71 to 290±72cm^2, P<0.001), with an associated significant increase in the range of PLA from maximum inspiration to end-expiration (ΔPLA) (83±40 to 117±36cm^2, P<0.001). Rate of change of PLA (ΔPLA/mean right and left diaphragm expiratory time) during expiration did not change significantly (22±15 to 23±8cm^2/s, P=0.87).

On review of both pre- and post-ELX/TEZ/IVA DCR and spirometry, PLA at full inspiration correlated strongly with height (pre, r=0.72, P<0.001; post, r=0.71, P<0.001) and moderately but significantly with FVC (r=0.69, P=0<0.001; post, r=0.55, P=0.005). ΔPLA correlated well with FEV$_1$ (pre, r=0.59, P=0.002; post, r=0.66, P<0.001) (Fig. 3).

There was no significant correlation between the magnitude of change (expressed either as percentage change, or as absolute values) of DCR variables and BMI, DCR variables and spirometry, or spirometry and BMI. No significant differences existed in ΔPLA (f [2,21] = 0.37, P = 0.70) or ppFEV$_1$ (f [2,21] = 0.70, P = 0.51) between those subjects naive to CFTR modulator therapy at the time of starting ELX/TEZ/IVA, those already taking TEZ/IVA prior to their first DCR, and those who commenced TEZ/IVA after first DCR and then changed to ELX/TEZ/IVA. Change in ΔPLA did not correlate significantly with the length of time between starting ELX/TEZ/IVA and second DCR imaging (r=0.4, P=0.06).

4. Discussion

We have shown that the novel measures of chest physiology provided by DCR significantly improved in pwCF started on triple combination CFTR modulator therapy. In particular, there were significant increases in the range of hemidiaphragm excursion and peak speed during deep breathing, peak speed during expiration, and a reduction in PLA after expiration and over the breathing cycle. These changes are consistent with improvement in FEV$_1$ and FVC, and are physiologically plausible. Whilst ELX/TEZ/IVA is known to improve FEV$_1$ by restoration of CFTR function, the precise mechanisms of its action on lung physiology are not. DCR may provide further evidence for this, and is shown here to be a useful tool for assessing pulmonary physiology in pwCF.

The reduction in PLA at full expiration suggests less air trapping as the lungs rest at a smaller volume after expiration, consistent with reduced FRC. DCR lung areas have been shown to predict FVC in other populations [14]. The increased peak speed of hemidiaphragm motion during expiration along with the greater range of ΔPLA over the breathing cycle suggests an improvement in the elastic recoil of the chest, as the chest rebounds faster and over a greater range after a deep breath. Previous work using oesophageal manometry has implicated loss of elastic recoil in airflow limitation in pwCF, [15] and decreased and slower diaphragm motion has previously been shown to be associated with more severe obstruction in people with chronic obstructive pulmonary disease [11]. The changes observed in this study may be due to improvement in sputum viscidity and volume post ELX/TEZ/IVA, [16] leading to less congested small airways and a reduction in the inflammatory milieu within the lung, thus improving its compliance. Indeed, many pwCF treated with triple therapy report a marked reduction in sputum volume and consistency [17]. The lack of significance of change in resting diaphragm position or maximum lung field area,

Table 2
pre/post-ELX/TEZ/IVA spirometric and DCR variables.

Manoeuvre	Variable	Units	PRE Mean	SD	POST Mean	SD	Corrected P-value
Spirometry	FVC	l	3.4	1.04	3.7	0.9	<0.001
	ppFVC		76.8	15.7	87.7	14.8	<0.001
	FEV_1	l	2.2	0.82	2.6	0.91	<0.001
	$ppFEV_1$		60.6	18.1	73.2	22.2	<0.001
	FEV_1/FVC		67.2	14.1	70.5	14.3	0.007
	BMI	kg/m^2	22.8	3.24	24.6	3.86	<0.001
Deep breathing	L deep distance*	mm	21.1	10.5	31.3	11.3	<0.001
	L deep in max speed	mm/s	28.2	11.1	37.3	16.1	0.02
	L deep out max speed	mm/s	21.1	9.79	30.8	18.7	0.078
	L deep out stop distance	mm	268	32.5	254	29	0.10
	L peak apex-diaphragm distance**	mm	292	31.2	286	31.4	0.54
	R deep distance	mm	17.5	10.8	25.5	9.44	<0.001
	R deep in max speed	mm/s	22.3	14.1	30.6	10.9	0.03
	R deep out max speed	mm/s	17.8	7.37	23.1	8.69	0.02
	R deep out stop distance	mm	262	31.9	247	31.8	0.08
	R peak apex-diaphragm distance	mm	282	33.4	273	31.5	0.16
Tidal breathing	R tidal distance	mm	11.2	3	13.6	5.67	0.10
	R tidal in max speed	mm	13.1	3.91	15.8	4.99	0.10
	R tidal out max speed	mm/s	13.3	5.38	13.7	3.9	0.87
	L tidal distance	mm/s	14.1	5.92	15.8	8.19	0.32
	L tidal in max speed	mm/s	15.3	4.43	17.5	6.53	0.20
	L tidal out max speed	mm/s	16	6.13	17	6.35	0.79
Lung areas	Max insp RL	cm^2	417	80.6	416	75	0.87
	Max exp RL	cm^2	334	71.5	299	72.1	0.001
	PLA change RL	cm^2	83	40	117	36.5	<0.001
	Rate of PLA change RL (expiration)	cm^2/s	22	15.3	22.5	7.98	0.87

* deep distance refers to the excursion of the diaphragm during deep breathing
** deep peak distance refers to the apex-diaphragm distance at full inspiration

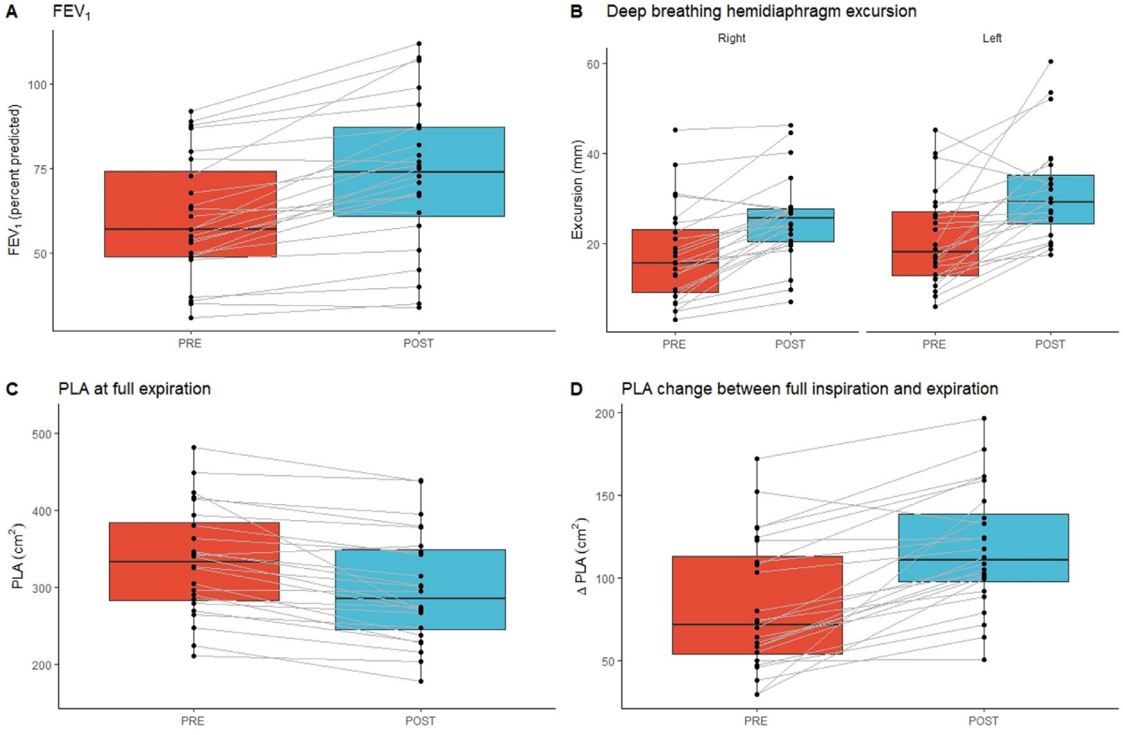

Fig. 2. Changes in $ppFEV_1$, diaphragm excursion and ΔPLA after initiation of ELX/TEZ/IVA therapy.

coupled with a larger range of ΔPLA, suggests that diaphragm position alone is not the sole contributing factor to (or consequence of) the reduction in lung size. These factors support the concept that triple therapy improves respiratory pump function.

DCR variables correlated with several spirometry variables, such as maximum lung area (PLA) with FVC, and ΔPLA with FEV_1, suggesting these DCR findings are plausible. FVC has been calculated from DCR images in other work looking at subjects with interstitial lung disease and has correlated expiratory lung areas with RV [14]. Further work is ongoing comparing DCR with plethysmography in the calculation of lung volume subdivisions in pwCF [18]. A significant improvement in BMI was also observed, which may have contributed to the improvement in diaphragm movement. Measures of abdominal obesity such as waist circumference, which might plau-

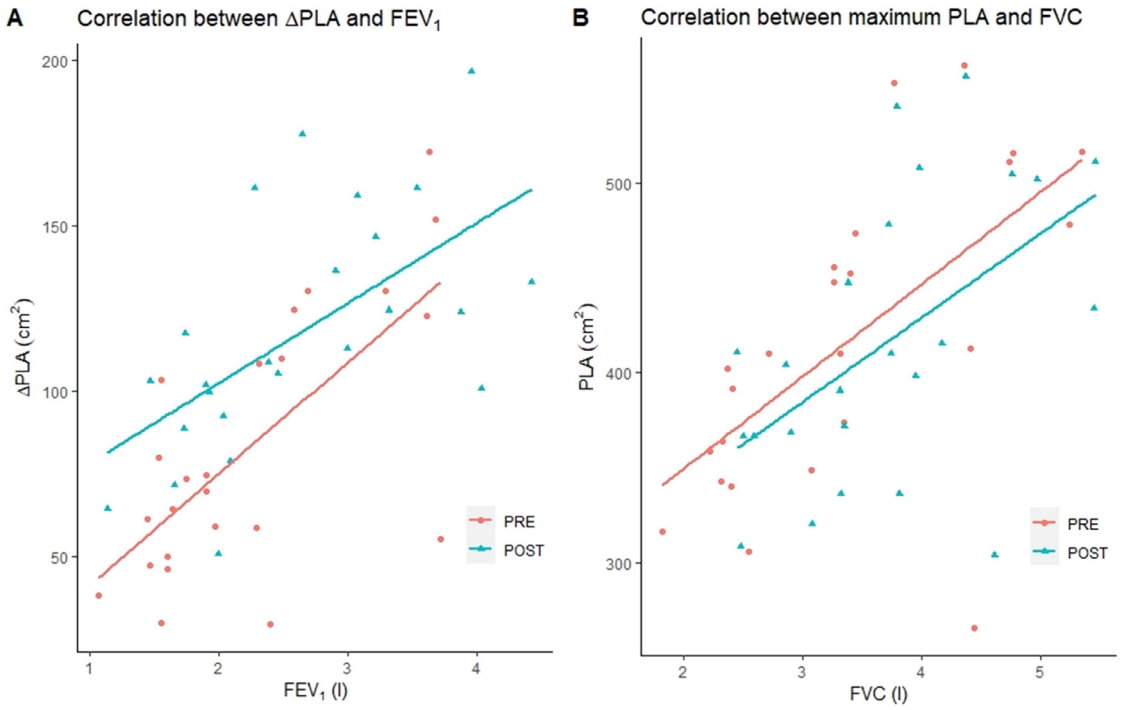

Fig. 3. Correlations between DCR metrics and spirometry.

sibly adversely affect diaphragm motion, were not recorded; further work may wish to address this.

The passive expiratory manoeuvre used in this study may better reflect the physiology of breathing compared to the forced manoeuvres performed in spirometry, or in other studies using DCR; however, the heterogeneity in DCR protocols used in the literature does limit the comparisons that can be made between this study and others using different DCR protocols [11,12].

There are limitations to our study. Since the bulk of data collection took place during the 2020 COVID-19 pandemic, the concomitant effect of the UK's national lockdown and shielding advice [19] may have impacted on the lung health of these individuals, although the similarity in improvement of spirometry lends plausibility to the observed effects being due to ELX/TEZ/IVA therapy. The reduction in routine face-to-face clinic attendance also prevented longitudinal spirometry and DCR imaging in this group, and significantly reduced the sample size of individuals with matched pre- and post-modulator DCR imaging. We were unable to utilize an untreated comparator group since at least 90% of pwCF are eligible for modulator therapy, and to withhold it would have been unethical. Also, although the variable treatment period prior to first DCR or after second DCR limits inferences about the effect size observed, a significant change in both spirometry and DCR metrics was observed in all individuals. Although some subjects were prescribed TEZ/IVA either before their first or second DCR, this is known to be less effective [1,2,20] and there were no significant differences in magnitude of change between these and CFTR-naive subjects. Several subjects did not complete full breathing manoeuvres, suggesting further refinement of the coaching given to individuals prior to DCR may be desirable.

In conclusion, this work demonstrates that DCR is a straightforward and useful tool to measure improvement in thoracic physiology and respiratory pump function following initiation of triple combination CFTR modulator therapy. Future studies are warranted to build on this exploratory work.

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Declaration of Competing Interest

No authors report any conflict of interest relevant to this work.

CRediT authorship contribution statement

Thomas S FitzMaurice: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft. **Caroline McCann:** Investigation, Data curation, Visualization. **Dilip Nazareth:** Supervision, Writing – review & editing. **Matthew Shaw:** Formal analysis. **Paul S McNamara:** Supervision, Writing – review & editing. **Martin J Walshaw:** Conceptualization, Supervision, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.01.007.

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