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

Thomas S FitzMaurice a,1,2, Caroline McCann b, Dilip Nazareth a,3, Matthew Shaw d, e, Paul S McNamara f, Martin J Walsh a, 3

a Adult CF Unit, Liverpool Heart and Chest Hospital, Thomas Drive, Liverpool L14 3PE, UK
b Department of Radiology, Liverpool Heart and Chest Hospital, Thomas Drive, Liverpool L14 3PE, UK
c Institute of Infection and Global Health, University of Liverpool, Liverpool, UK
Research Unit, Liverpool Heart and Chest Hospital, Thomas Drive, Liverpool L14 3PE, UK
Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool, UK
b Institute in the Park (University of Liverpool), Alder Hey Children’s Hospital, Liverpool, UK
d Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK

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: In the 24 pwCF group, we found significant improvements in both the right (18±11 to 26±9 mm, P<0.001) and left (21±11 to 31±11 mm, P<0.001) hemidiaphragm, 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±72cm², P<0.001), with a significant increase in ΔPLA (83±40 to 117±36cm², 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.

© 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 license (http://creativecommons.org/licenses/by/4.0/)

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
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 enrolled 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 enrolled 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 (±10%) from their yearly average were excluded, as were those enrolled 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 ELX/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 2000DR 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 Spirostitik™ 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 ± 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...
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 naïve 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 1
demographic and anthropometric characteristics of subjects.

| Characteristic | Number (%) |
|----------------|------------|
| Female         | 11 (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)      |
| Age (years)     | Pre: 27±6 Post: 28±6 |
| Height (cm)     | 167±10     |
| Weight (kg)     | 64±11      |
| BMI (kg/m²)     | 23±3       |

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=0.001; post, r=0.55, P=0.005). ∆PLA correlated well with FEV₁ (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 ∆PLA (f [2,21] = 0.37, P = 0.70) or ppFEV₁ (f [2,21] = 0.70, P = 0.51) between those subjects naïve 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 ∆PLA 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 FEV₁ and FVC, and are physiologically plausible. Whilst ELX/TEZ/IVA is known to improve FEV₁ 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 ∆PLA 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 viscosity 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,
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 FEV₁, 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-

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

| Maneuver          | 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               | l        | 76.8     | 15.7 | 87.7      | 14.8 | <0.001            |
|                   | FEV₁                | l        | 2.2      | 0.82 | 2.6       | 0.91 | <0.001            |
|                   | ppFEV₁              | l        | 60.6     | 18.1 | 73.2      | 22.2 | <0.001            |
|                   | FEV₁/FVC            | l        | 67.2     | 14.1 | 70.5      | 14.3 | 0.0007            |
|                   | BMI                 | kg/m²    | 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  | 0.07              |
|                   | 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         | cm²      | 417      | 80.6 | 416       | 75   | 0.87              |
|                   | Max exp RL          | cm²      | 334      | 71.5 | 299       | 72.1 | 0.001             |
|                   | PLA change RL       | cm²      | 83       | 40    | 117       | 36.5 | <0.001            |
|                   | Rate of PLA change RL (expiration) | cm²/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 ppFEV₁, diaphragm excursion and ΔPLA after initiation of ELX/TEZ/IVA therapy.
ibly 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-naïve 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.

Funding information

No external funding was sought for this work.

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.

Acknowledgements

All authors have reviewed the manuscript.

Supplementary materials

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

References

[1] Taylor-Cousar JL, Munck A, McKone EF, Van Der Ent CK, Moeller A, Simard C, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del. New england journal of medicine. 2017;377(21):2013–23.
[2] Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, et al. Tezacaftor–ivacaftor in residual-function heterozygotes with cystic fibrosis. N Engl J Med 2017;377(21):2024–35.
[3] Middleton PG, Mall MA, Drevinek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med 2019;381(19):1809–19.
T.S. FitzMaurice, C. McCann, D. Nazareth et al.  
Journal of Cystic Fibrosis 21 (2022) 1036–1041

[4] Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elixacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet 2019;394(10212):1940–8.

[5] Divangahi M, Balghi H, Danialou G, Comtois AS, Demoule A, Ernest S, et al. Lack of CFTR in skeletal muscle predisposes to muscle wasting and diaphragm muscle pump failure in cystic fibrosis mice. PLoS Genet 2009;5(7):e1000586.

[6] Enright S, Chatham K, Ionescu AA, Unnithan VB, Shale DJ. The influence of body composition on respiratory muscle, lung function and diaphragm thickness in adults with cystic fibrosis. J Cyst Fibros 2007;6(6):384–90.

[7] Crowley C, Connor OJO, Ciet P, Tiddens H, Maher MM. The evolving role of radiological imaging in cystic fibrosis. Curr Opin Pulm Med 2021;27(6):575–85.

[8] Goralski JL, Stewart NJ, Woods JC. Novel imaging techniques for cystic fibrosis lung disease. Pediatr Pulmonol 2021;56(5):540–54.

[9] Stanojevic S, Ratjen F. Physiologic endpoints for clinical studies for cystic fibrosis. J Cyst Fibros 2016;15(4):416–23.

[10] Hino T, Hata A, Hida T, Yamada Y, Ueyama M, Araki T, et al. Projected lung areas using dynamic X-ray (DXR). European Journal of Radiology Open 2020;7:100263.

[11] Hida T, Yamada Y, Ueyama M, Araki T, Nishino M, Kurosaki A, et al. Decreased and slower diaphragmatic motion during forced breathing in severe COPD patients: Time-resolved quantitative analysis using dynamic chest radiography with a flat panel detector system. Eur J Radiol 2019;112:28–36.

[12] Hida T, Yamada Y, Ueyama M, Araki T, Nishino M, Kurosaki A, et al. Time-resolved quantitative evaluation of diaphragmatic motion during forced breathing in a health screening cohort in a standing position: Dynamic chest phrenicography. Eur J Radiol 2019;113:59–65.

[13] FitzMaurice TS, McNamara PS, Nazareth D, McCann C, Bedi R, Shaw M, et al. Utility and validity of dynamic chest radiography in cystic fibrosis (dynamic CF): an observational, non-controlled, non-randomised, single-centre, prospective study. BMJ Open Respiratory Research 2020;7(1):e000569.

[14] Ueyama M, Hashimoto S, Takeda A, Maruguchi N, Yamamoto R, Matsumura K, et al. Prediction of forced vital capacity with dynamic chest radiography in interstitial lung disease. Eur J Radiol 2021;142:109866.

[15] Zapletal A, Desmond KJ, Demizzo D, Coates AL. Lung recoil and the determination of airflow limitation in cystic fibrosis and asthma. Pediatr Pulmonol 1993;15(1):13–18.

[16] Morrison CB, Shaffer KM, Araba KC, Markovetz MR, Wykoff JA, Quinney NL, et al. Treatment of cystic fibrosis airway cells with CFTR modulators re- verses aberrant mucus properties <em>via</em> hydration. Eur Respir J 2021:2100185.

[17] Martin C, Burnet E, Ronayette-Preira A, de Carli P, Martin J, Delmas L, et al. Patient perspectives following initiation of elixacaftor-tezacaftor-iva- caftor in people with cystic fibrosis and advanced lung disease. Respir Med Res 2021;80:100829.

[18] FitzMaurice TS, Nazareth D, McCann C, Walsh M, McNamara PS. P102 Utility of Dynamic Chest Radiography (DCR) for calculating lung volume subdivisions in adult people with cystic fibrosis. J Cyst Fibros 2021;20:570.

[19] Knietowicz Z. Covid-19: Highest risk patients are asked to stay at home for 12 weeks. BMJ 2020;368:m1170.

[20] Munck A, Kerem E, Ellermunter H, Campbell D, Wang LT, Abugwalla N, et al. Tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for minimal function CFTR mutations. J Cyst Fibros 2020;19(6):962–8.