Case Report

The Effect of Ivacaftor in Adolescents with Cystic Fibrosis (G551D mutation): An Exercise Physiology Perspective

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ABSTRACT

Purpose: The purpose of this report was to evaluate the influence of 12 weeks of ivacaftor treatment on the aerobic function of 2 teenage patients with cystic fibrosis (CF; ΔF508/G551D) using a maximal cardiopulmonary exercise test.

Summary of Key Points: One patient, with relatively mild disease, demonstrated no clinically meaningful changes in maximal oxygen uptake ($\dot{V}O_{2max}$). However, in the second case, with more established lung disease on imaging, $\dot{V}O_{2max}$ improved by approximately 30%, an improvement out of proportion with early lung function changes. This improvement resulted from increased muscle oxygen delivery and extraction.

Statement of Conclusions: Cardiopulmonary exercise testing can monitor the extent and cause(s) of change following interventions such as ivacaftor, with the potential to identify functional changes independent from spirometry indices.

Recommendations for Clinical Practice: Cardiopulmonary exercise testing represents an important and comprehensive clinical assessment tool, and its use as an outcome measure in the functional assessment of patients with CF is encouraged.

Key words: adolescent, cardiopulmonary exercise test, cystic fibrosis, drug therapy, exercise/physiology.

INTRODUCTION

Cystic fibrosis (CF) is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Traditional therapies focus on alleviating manifestations secondary to CFTR dysfunction. A new oral treatment (ivacaftor , Vertex Pharmaceuticals, Boston, Massachusetts) has been licenced specifically for those with the G551D-CFTR mutation. Ivacaftor, a CFTR "potentiator", increases the open time of activated CFTR at the cell surface, restoring chloride-transport activity of the G551D-CFTR protein[1].

To date, sustained improvements in quality of life, incidence of pulmonary exacerbations, respiratory symptoms, pulmonary function, weight, and biomarkers of CFTR activity (sweat chloride and nasal potential difference) have been reported following treatment with ivacaftor in patients that are heterozygous for the G551D mutation with mild-to-moderately impaired lung function, without substantial adverse effects[2,3,4,5]. More recently, administration of ivacaftor has also revealed clinical improvements in severely ill patients[6] and a G551D homozygote[7].

Although common clinical assessments such as spirometry and body weight provide key endpoints for the evaluation of new CF treatments, their sensitivity to detect change in early disease has been questioned[8]. Furthermore, measurements of lung function cannot accurately predict patients' exercise capacity. Aerobic fitness (maximal oxygen uptake, $\dot{V}O_{2max}$) is of particular clinical importance in patients with CF given its association with longevity[9,10], quality of life[11] and reduced risk of hospitalization[12]. However, exercise testing as an outcome in both physical therapy practice and therapeutic trials remains in its infancy[13]. Understanding how the clinical alterations evident following pharmacological or physical therapy treatment translate to patients' physical function is important.

Only 1 previous study investigating the effects of ivacaftor has incorporated an exercise testing measure[7], documenting a 292% (+410 m) improvement from baseline in the distance achieved during the 6-minute walk test in a female adult (G551D homozygote) following 12 months of treatment. Although tests such as this are common practice within physical therapy for individuals with CF, a number of methodological issues accompany these crude tests, which must be considered when used in this context. First, these tests are often subjective and submaximal in nature and fail to quantify physiologically a maximal effort. Second, the derived parameters are limited to heart rate and arterial oxygen saturation, which are often not presented and do not provide physiological data to support the mechanism(s) responsible for any observed change.

Maximal cardiopulmonary exercise testing (CPET), incorporating measurement of gas exchange, provides the most precise measurement of aerobic fitness. Much of the value of CPET resides in its capacity to describe the integrated function of the pulmonary, cardiovascular and muscular systems during exercise. Moreover, in addition to $\dot{V}O_{2max}$, additional key parameters of aerobic exercise function can also be obtained, such as the O_2 cost of exercise (exercise efficiency)[14]. In response to the European CF Society (ECFS) Clinical Trials Network Standardization Committee's call to assess the validity, reproducibility and feasibility of outcome measures to be used in CF, a valid protocol for use with young patients with CF was recently presented[15]. Furthermore, the typical error associated with the derived outcome measures has since been presented[16], enabling meaningful change from therapeutic or physical therapy interventions to now be ascertained. However, to our knowledge there are no reports of effect of ivacaftor on patients' aerobic fitness assessed using the reference standard CPET.

The purpose of this report was to provide novel data from CPET in 2 teenage patients with cystic fibrosis (ΔF508/G551D) treated with ivacaftor to demonstrate *(1)* the effects of

ivacaftor on aerobic function and *(2)* the possible factor(s) modulating this response. By answering these questions, the report will provide novel data on the utility and feasibility of CPET as a clinical outcome measure.

CASE DESCRIPTION

Participants

Case A: A 14 y old female climbing enthusiast had presented with neonatal meconium ileus requiring bowel resection. She suffered a complicated clinical course, with early *Pseudomonal* and then *Stenotrophomonal* respiratory infections, allergic bronchopulmonary aspergillosis, and more recently *Mycobacterium abscessus* infection that could not be eradicated. Despite preserved lung function (forced expiratory volume in 1 second (FEV_1)) 92% predicted), thoracic high-resolution computed tomography (HRCT) detailed extensive bronchiectasis and consolidation in right middle and lingual lobes (Fig. 1A). Body mass index (BMI) was 20.3 $kg \cdot m^2$ (> 50^{th} centile). Sweat chloride measured 104 $mmol \cdot L^{-1}$ pretreatment. Routine maintenance medications included the following: pancrelipase (10 000 and 40 000 in various combinations with meals and snacks), vitamin E (200 units alternate days), vitamin A and D gel (1 daily), ursodeoxycholic acid (450 mg twice daily), polyethylene glycol solution (1 sachet daily), azithromycin (500 mg daily), doxycycline (100 mg once daily), meropenem (nebuliser 250 mg twice daily), dornase alpha (nebulizer 2.5 mg once daily), hypertonic saline (7% nebulized [4 ml] once or twice daily with physical therapy), beclomethasone (200 μg twice daily via spacer), salbutamol (2-4 puffs when required for wheezing), and amphotericin (nebulized 20 mg alternate days, nonliposomal formulation).

Case B: An active 16-year-old male presented at the age of 16 months with recurrent respiratory infections and failure to thrive. He has suffered recurrent *Pseudomonal* infections from an early age but has remained well with aggressive treatments (FEV_1 108% predicted). Thoracic HRCT showed widespread bronchiectatic changes but without significant consolidation (Fig. 1B). BMI was 19.7 $kg \cdot m^2$ (50^{th} centile). Sweat chloride measured 107 $mmol \cdot L^{-1}$ pretreatment. Routine maintenance medications included the following: pancrelipase (10 000 and 40 000 in various combinations with meals and snacks), vitamin A and D gel caps (3 daily), vitamin E (200 units daily), vitamin K (10 mg daily), Fortisip Compact nutritional supplement (with Creon 2 daily), colomycin (nebulized 2 mega units mixed with gentamicin 80 mg twice daily), dornase alpha (nebulized 2.5 mg once daily), flucloxacillin (500 mg twice daily).

Description of Intervention

The main goal of this intervention was to assess the influence of orally administered ivacaftor treatment (150 mg 12 hourly) on CPET-derived measures of aerobic function in 2 young patients with CF in conjunction with common clinical outcome measures. To monitor the effects of treatment, the 2 teenage patients, both compound heterozygotes (G551D/ΔF508), underwent routine clinical assessments for a 20-week duration.

In addition to this, CPET was performed before and after (6 and 12 weeks) initiating orally administered ivacaftor treatment to assess whether any change in aerobic function was evident and, if so, the physiological factor(s) responsible for this. These time points for reassessment were implemented to enable comparison of intervention-induced changes with the typical error of the CPET measurements established in this patient population over this time period to identify clinically meaningful changes[16]. The patients continued their normal maintenance medications as required and continued with their typical physical activity and

nutritional intake patterns. Additional measurements of central (O_2 delivery) and peripheral (O_2 extraction/ utilization) factors that can influence $\dot{V}O_{2max}$ were also obtained to understand the mechanism(s) responsible for any change.

Maximal Cardiopulmonary Exercise Testing.

Participants were instructed to arrive at the exercise laboratory in a rested state, 2 hours or more postprandial and having refrained from caffeine for 2 hours or more. Following thorough familiarization with the equipment and requirements of the visit, a maximal CPET was performed on a cycle ergometer [Lode Excalibur or Lode Corival, Groningen, The Netherlands]. A single-session protocol, encompassing a ramp incremental test (10-25 $W \cdot min^{-1}$) and a supramaximal (110% peak power output [PPO]) verification phase (S_{max}) that has been validated in this patient population[15] was used. Following a 3-minute warm-up (20 W cycling), the incremental ramp test was completed until exhaustion whilst pedalling between 70 to 80 revolutions per minute. Exhaustion was defined as a drop in pedal speed of more than 10 revolutions per minute for 5 consecutive seconds, despite strong verbal encouragement. Participants then completed 5-minute active recovery (20 W cycling) and 10-minute passive seated recovery before completing the S_{max} verification test. S_{max} involved a 3-minute warm-up (20 W cycling), an exhaustive "step" transition to a constant work rate equivalent to 110% PPO from the ramp test, followed by 5-minutes active recovery (20 W cycling).

Assessment Methods

Anthropometry and pulmonary function. Body mass (Seca 220; Vogel & Halke, Hamburg, Germany) and stature (Seca 220; Vogel & Halke, Hamburg, Germany) were measured to the nearest 0.01 kg and 0.01 m, respectively. FEV_1 and forced vital capacity

(FVC) were assessed using spirometry (MicroMedical MicroLoop 3535). The best of three consistent (< 5% variability) exhalations was documented and expressed as a percentage of predicted reference data.[17]

Pulmonary gas analysis. Prior to each exercise test, a metabolic cart (Metalyzer 3B Cortex, Biophysik, Leipzig, Germany) was calibrated using gases of known concentration, and the turbine volume transducer using a 3 L calibration syringe (Hans Rudolph, Kansas City, MO). Breath-by-breath pulmonary gas exchange and ventilation were measured and averaged to 15-second time bins. The highest 15-second stationary average $\dot{V}O_2$ from the combined ramp and supramaximal exercise tests (described later) was taken to represent $\dot{V}O_{2max}$, a safe and appropriate $\dot{V}O_{2max}$ verification criterion in this population.[15] The primary outcome measure, given its clinical important in CF, was $\dot{V}O_{2max}$. However, additional submaximal parameters of aerobic fitness were also derived. The lactate threshold was noninvasively identified using the gas exchange threshold (GET)[18] and confirmed through visual inspection of the ventilatory equivalents for $\dot{V}O_2$ and $\dot{V}CO_2$. The $\dot{V}O_2$ "gain" ($\Delta\dot{V}O_2/\Delta WR$), a measure of exercise efficiency, was determined by regression of the "linear" portion of the $\dot{V}O_2$ response against power output.

Additional mechanistic measures: Thoracic bioelectrical impedance (PhysioFlow, PF-05, Manatec Biomedical, Paris, France), which has been validated in CF,[19] was used to noninvasively measure beat-by-beat heart rate (HR), stroke volume (SV) and cardiac output ($\dot{Q}$), which was subsequently averaged to 15-second time intervals. Arterial-venous O_2 context difference ($C_{(a\text{-}\bar{v})}O_2$), a measure of O_2 extraction, was estimated via rearrangement of the Fick equation:

$$(C_{(a\text{-}\bar{v})}O_2) = \frac{\dot{V}O2}{\dot{Q}}$$

Arterial O_2 saturation at the fingertip (SpO_2) was measured on a beat-by-beat basis via pulse oximetry (NONIN, Avant 4000, NONIN Medical Inc., USA). Subjective ratings of perceived exertion (RPE) and dyspnea (RPD) were recorded upon exhaustion using methodology described elsewhere.[15,16] All procedures and protocol were approved by the institutional ethics committee and informed parental consent and participant assent were obtained prior to the commencement of the study.

OUTCOMES

The 2 patients' clinical and exercise characteristics at baseline and in response to 12 weeks of treatment with ivacaftor are presented in Table 1. Figure 2 presents the percentage change in BMI, FEV_1 and $\dot{V}O_{2max}$ during 12 weeks of treatment. BMI and FEV_1 were then monitored during follow-up up to week 20. The magnitude of change in these measurements is presented in relation to the established typical error of measurement using these procedures over a 4-6 week period[16]. All exercise testing was well tolerated with no adverse events, and all tests satisfied the criteria for the provision of a maximal effort. However, case B reported to his 12 week CPET feeling fatigued.

Case A

This patient experienced 2 successive upper respiratory tract infections (URTI) (weeks 3 and 10) during treatment. Despite this, her lung function and body weight were maintained when she would typically deteriorate. Following the first 6 weeks of treatment, her weight had increased from 48.5 kg to 50.5 kg, while predicted FEV_1 increased from 92% to 96%. A fall in her sweat chloride (104 to 21 $mmol \cdot L^{-1}$) was noted at this time point. Following 6 weeks of treatment her body mass normalized $\dot{V}O_{2max}$ had increased by 6.4% from baseline, which was

not considered clinically a meaningful improvement since it resides within the typical error of this measurement[16]. End-exercise SpO_2 upon exhaustion increased from 92% to 96%. Because of a combination of leg fatigue (9 out of 10) and dyspnea (rating of 7 out of 10) CPET was terminated.

At the 12-week assessment, subjectively she reported feeling better and more "energetic" and was slightly more productive with airway clearance physiotherapy. Her $FEV_{1\%}$ and weight showed moderate though convincing increases (+4.7% relative and +1.7 kg, respectively). A small increase in sweat chloride (21 to 35 $mmol \cdot L^{-1}$) was evident. Although there was minimal influence upon PPO, subjective ratings of exertion and dyspnea or the additional submaximal parameters of aerobic fitness (GET and $\dot{V}O_2$ gain) at this time point, her body mass normalized $\dot{V}O_{2max}$ had increased by 30.3% from pretreatment baseline. This substantial increase was deemed clinically meaningful since the change over this 6 week period exceeded the typical error (13.3%) of measurement established over this duration[16]. Furthermore, end-exercise SpO_2 had improved to 98% from 95% pretreatment. By this point, her PPO had also increased by 9.0% (12 W) and her rating of dyspnea had improved from 7 to 5. Little change was detected in the submaximal parameters of aerobic fitness.

Of the factors which can affect patient A's $\dot{V}O_{2max}$, a change was observed in both central (O_2 delivery) and peripheral (O_2 extraction) indices. With regard to O_2 delivery, a slight reduction in HR was evident at weeks 6 and 12 (205 $beats \cdot min^{-1}$ to 202 $beats \cdot min^{-1}$ at both tests). However, since SV was increased at both time points [52 $mL \cdot beat^{-1}$ to 56 (+7%) and 60 (+15%) $mL \cdot beat^{-1}$], $\dot{Q}$ was improved as a consequence [10.6 $L \cdot min^{-1}$ to 10.8 and 11.6 $L \cdot min^{-1}$ (+2% and +9%, respectively)]. Arterial O_2 desaturation upon exhaustion was also reduced during the 12 weeks of treatment, with SpO_2 rising from 92% to 96% and 98% at weeks 6 and 12, respectively. Estimated O_2 extraction ($C_{(a-\bar{v})}O_2$) was also increased at both week 6 [+1 $mL \cdot min^{-1} \cdot 100mL$ (+ 8%) and week 12 [+3 $mL \cdot min^{-1} \cdot 100mL$ (+ 23%)]. This

change in physiological function detected through CPET following 12 weeks of treatment preceded the later rise detected in FEV_1 (+19% from baseline) following 20 weeks (Figure 2). Her weight also increased further to 52.4 kg (+3.9 kg from baseline) at this stage.

Case B

This patient was clinically well throughout treatment and body weight and lung function remained stable. Following 6 weeks of treatment, his weight remained stable at 58.3 kg while lung function (FEV_1) improved from 108% to 112% predicted. A notable fall in sweat chloride (107 to 58 $mmol \cdot L^{-1}$) was also evident in this patient at this time point. A modest improvement in his body mass normalized $\dot{V}O_{2max}$ from baseline was evident (+3.4%); however, this was not considered clinical meaningful. End-exercise SpO_2 was unchanged at 96% and CPET was terminated because of both leg fatigue (RPE of 9) and dyspnea (RPD of 7).

Following 12 weeks of treatment, he reported feeling clinically well; however he was tired because of heavy school and football workloads over the preceding weeks. In a patient who has difficulty maintaining weight, he had gained 0.5 kg by week 12. FEV_1 had also increased from 108% predicted at baseline to 120% predicted and sweat chloride concentration has reduced further to 43 $mmol \cdot L^{-1}$. Although PPO increased by 9% from baseline (20 W) and SpO_2 at exhaustion had improved from 96% to 98%, his body mass normalized $\dot{V}O_{2max}$ was marginally reduced (-5.1% from baseline) as were the submaximal indicators of aerobic fitness. However, this should not be considered a true impairment of aerobic function as it is within the typical error of these measurements[16]. While his perceived dyspnea upon exhaustion was higher (7-9), RPE remained stable at 9.

Although modest improvement was observed in his systemic O_2 delivery (cardiac output and SpO_2), this appeared to fluctuate around baseline. Maximal $\dot{Q}$ was 19.0 $L \cdot min^{-1}$ at

baseline and then 15.5 and 18.2 $L \cdot min^{-1}$ following 6 and 12 weeks of treatment, respectively. HR and SV remained relatively stable at week 6 (-3 $beats \cdot min^{-1}$ and +5 $mL \cdot beat^{-1}$, respectively). However, at 12 weeks his SV was increased to 104 $mL \cdot beat^{-1}$ and maximal HR was substantially lower at 175 $beats \cdot min^{-1}$, meaning $\dot{Q}$ was not particularly influenced. Furthermore, following increased extraction at 6 weeks (+3 $mL \cdot min^{-1} \cdot 100mL$), this was near baseline by week 12 (-0.2 $mL \cdot min^{-1} \cdot 100mL$). No clinically significant change in SpO_2 was observed. Continued clinical monitoring to week 20 then revealed a steady increase in weight to gain 3.2 kg from baseline and increase the relative change from baseline in $FEV_{1\%}$ predicted to 6.7%.

DISCUSSION

The aim of this case report was to describe the effects of orally administered ivacaftor on the aerobic exercise function and clinical profile of 2 teenage patients with CF (A, 14 y old female; B, 16 y old male) who were heterozygous for the G551D mutation. Furthermore, this report aimed to demonstrate the utility of CPET as a clinical outcome measure. Following 12 weeks of treatment with ivacaftor, both patients showed substantial improvements in sweat chloride. Despite patient A experiencing 2 successive URTIs, lung function and body weight were maintained when she would typically deteriorate. Patient B was clinically well throughout treatment, with his body weight and lung function stable throughout. Following 12 weeks of treatment, no meaningful change was observed in $\dot{V}O_{2max}$ in patient B. In patient A, however, $\dot{V}O_{2max}$ increased by 30.3%, which should be considered clinically meaningful because it is 20% greater than the 4 to 6 week typical error associated with this measurement. This improvement resulted from both enhanced muscle O_2 delivery and muscle O_2 extraction.

There could be numerous explanations for the varied response observed between these patients. Firstly, at outset, both patients presented with mildly impaired lung function.

However, Case A's lung function was a little lower, evidence of active underlying infection with *M. Abscessus* was present and thoracic HRCT identified more severe lung damage with patchy parenchymal inflammatory changes. Although established lung damage cannot directly be rectified, this patient may well have had more to gain from this new, transformational treatment. In an earlier ivacaftor clinical trial cohort[3], improvements in sweat chloride and FEV_1 were seen to plateau after 2 weeks. Because case B's lung function at baseline was higher than the patients in this initial study by Ramsey *et al.*[3], this may explain why a plateau was observed in his response.

Conceivably, an individual ceiling effect for $\dot{V}O_{2max}$ improvements may exist, whereby relatively fit patients have less to gain in the absence of exercise training, and that case B's original fitness status resided around this threshold. As such, case A's $\dot{V}O_{2max}$ normalized to body mass was lower than case B at baseline, of which gender difference may be a factor. An impact of overreaching or chronic fatigue in case B also cannot be excluded. Although a higher PPO was documented, this patient reported to the exercise laboratory for his week 12 CPET feeling tired, due to school and football workloads. His lower maximal heart rate (~20 beats·min^{-1}) compared with his previous CPETs may support this. Interestingly, this reduced response has previously been observed in this patient when he previously performed 2 CPETs over a short-term period. This stresses the importance of CPET standardization when interpreting "true" physiological changes in results. Although measures of O_2 delivery, extraction and minimum SpO_2 in this patient all fluctuated around baseline, without meaningful change, SV was elevated following 12 weeks. However, given that maximal HR was lower, his resulting $\dot{Q}$ was not increased.

To our knowledge, the only existing evidence of ivacaftor's effect upon aerobic fitness was demonstrated in a 19-year-old G551D homozygote with poor lung function using the 6-minute walk test [292% (+ 410 m) improvement from baseline)[7]. However, in contrast

to this study, the shuttle walk assessment by Harrison *et al.*[7] was undertaken following 12 months of treatment. However, although only presented graphically, the authors' figure indicate that exercise testing was also performed at approximately 2 and 10 weeks. Interestingly, the majority of the patient's improvement in aerobic fitness occurred within the time period spanning these 2 time points (~ +225 m (week 2) and ~ +310 m (week 10) from baseline, respectively). Only further longitudinal study would confirm the inter-patient variability observed within the present case report and determine whether ivacaftor could sustain patients' aerobic fitness following initial improvements. However, data from the Harrison *et al.*[7] study are promising, presenting a modest but steady improvement from approximately 10 weeks to 52 weeks of treatment. Of additional interest is the relatively fixed status of the submaximal indices of aerobic function ($GET_{\%}$ and $\dot{V}O_2$ gain) in contrast to the acute improvement in maximal oxygen uptake. Whether these parameters respond over a longer duration warrants further exploration.

The data from this study are clinically useful for a number of reasons. Firstly, they are novel data regarding the mechanisms by which ivacaftor may enhance patients' physiological function during exercise. The magnitude of change in this patient was particularly impressive given that *1)* she was in a state of URTI during the majority of her treatment, *2)* improvements cannot simply be attributable to a learning effect or initial submaximal effort, because both patients were thoroughly familiarized with the protocol that encompasses a verification phase to confirm "true" $\dot{V}O_{2max}$[15]; and *3)* no exercise training intervention was undertaken outside the patients' typical physical activity routine.

Sparse data exists concerning the magnitude of change in $\dot{V}O_{2max}$ of young patients with CF following pharmacological or exercise interventions. To date, only 1 previous study has demonstrated a meaningful improvement in $\dot{V}O_{2max}$ in young patients with CF and this was following an intense 6-week period of exercise training. Hulzebos *et al.*[20] reported a

"meaningful" improvement (19%), following a high-intensity cycling exercise training programme. This training intervention resulted in an indication of enhanced O_2 delivery to the active muscle tissue, evidenced by the O_2 pulse. It was suggested that O_2 extraction was also influenced; however, only data for the $\dot{V}O_2$ gain was presented, which provides a measure of submaximal O_2 consumption and exercise efficiency.

An additional important purpose of the present report was to demonstrate the utility of CPET to make inferences regarding therapeutic interventions or disease-related changes. Although case A reported feeling better and more "energetic" at week 12, no clinical improvement was detected using standard spirometric indices until week 20. However, CPET did document substantial improvement in her physiological function. The fact that her $\dot{V}O_{2max}$ improvement was out of proportion with early lung function changes, although the latter did pick up during extended follow-up, demonstrated the capacity of this integrated testing to detected subtle changes in patients that are relatively well earlier than common clinical outcomes. Furthermore, although more common clinical exercise tests are often cost-effective and easily conducted, a CPET can provide a wealth of mechanistic information that cannot be derived from standard clinical assessments or crude exercise tests such as shuttle walk or step protocols. In addition, although such tests can be used to estimate $\dot{V}O_{2max}$, they are likely to underestimate aerobic fitness and cannot truly verify a maximal effort. Owing to its merits, the ECFS Exercise Working Group recently promoted CPET as the exercise testing method of choice where possible for this patient group.

Aerobic fitness is an important clinical parameter in CF and should become an important outcome within the physical therapy assessment of patients. Although the present report focused on the utility of CPET to assess the response to ivacaftor, more common practices such as intravenous antibiotics (IVABs) and physical therapy interventions warrant detailed assessment. For example, the present patient reporting feeling more energized is a

common response during treatment with IVABs, particularly electively. However, patients must often continue treatment until a change in lung function is observed. CPET may provide a more sensitive outcome measure to detect subtle changes earlier.

It is acknowledged that case study data are limited in its generalizability to the wider patient population. Furthermore, the follow-up time was relatively short and it would have been of interest to have performed CPET at week 20. In addition, no measurements of habitual physical activity were obtained to see whether improved exercise capacity translated into increased levels of physical activity.

Given the ongoing change in stance from the European Cystic Fibrosis Society regarding the clinical relevance of CPET in CF, it is likely that this will become a routine assessment method over the coming years. If more physical therapists involved in the management and treatment of this condition can adopt this form of testing, this would be of great benefit. It is hoped that this study demonstrates how insightful and relatively straightforward CPET is and will encourage more physical therapists to adopt it in clinical practice and as an investigative tool.

CONCLUSION

These cases demonstrate that not only does ivacaftor have a substantial beneficial effect on the sweat chloride of patients with CF and the G551D mutation, but clinically meaningful improvement in aerobic fitness can also be observed in the absence of exercise training. These changes manifest earlier than current clinical outcomes and result from both improved muscle O_2 delivery and extraction during exercise. However, a fitness threshold may exist whereby patients who are relatively fit experience less or no improvement. Importantly, this case review highlights that CPET can provide an additional important clinical outcome measure to assess functional change and with this the mechanism(s) responsible for change.

CPET can detect substantial changes in aerobic fitness, which may occur independently from adaptations in pulmonary function, as was evidenced in 1 of the present patients. To objectively quantify the influence of pharmacological or physical therapy interventions on patients' physiological function, the use of CPET is encouraged. CPET should be included within future, long-term research demonstrating its utility within physical therapy practice, pharmacological or exercise interventions.

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FIGURE LEGENDS

Figure 1. High-resolution computed tomography images for case A and case B pretreatment with orally administered ivacaftor. Case A microbiology: *Mycobacterium abscessus, Stenotrophomas maltophilia,* allergic bronchopulmonary aspergillosis in remission. Case B microbiology: Intermittent *Pseudomonas Aeruginosa* and previous *Achromobacter xylosoxidans.*

Figure 2. Percentage change from baseline in body mass index, forced expiratory volume in 1 second (percentage predicted[17]) and body mass normalized $\dot{V}O_{2max}$ in 2 patients with cystic fibrosis patients (CF) with the G551D-CFTR mutation [A (14 y female; ● black circles) and B (16 y male; ○ white circles)] at the start of ivacaftor (day 0) and following 6, 12 and 20 weeks of treatment. Exercise testing was not performed at 20 weeks and the magnitude of change is presented in relation to the typical error of measurements in young patients with CF over a 4- to 6-week period[16].

FIGURES

Figure 1

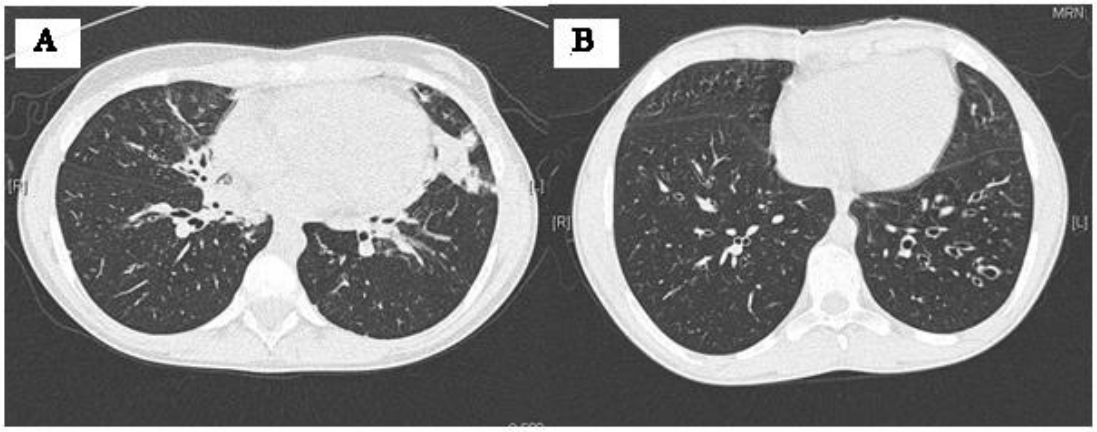
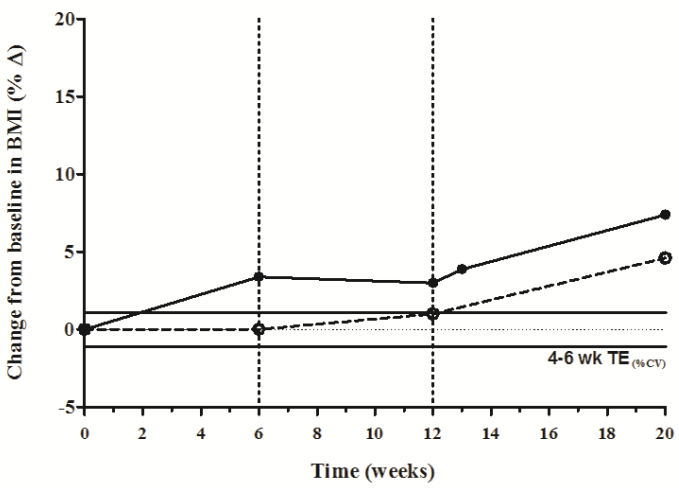
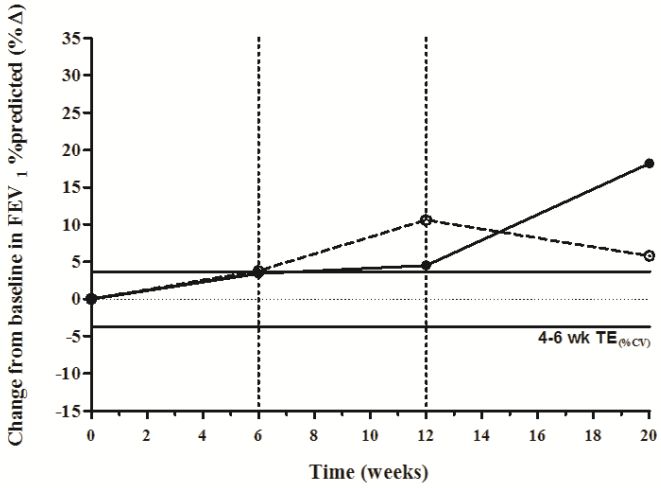
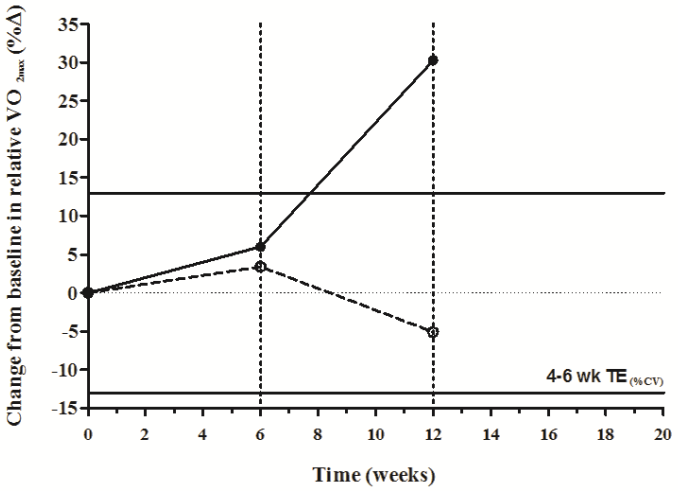


Figure 2


Change from baseline in BMI (% Δ)
Time (weeks)
4-6 wk TE(%CV)


Change from baseline in FEV 1 %predicted (% Δ)
Time (weeks)
4-6 wk TE(%CV)


Change from baseline in relative VO 2max (%Δ)
Time (weeks)
4-6 wk TE(%CV)

TABLES

Table 1. The clinical and exercise-based response of 2 pediatric cystic fibrosis patients (A, 14 y female; B, 16 y male) with the ΔF508/G551D mutation to 6 and 12 weeks of oral ivacaftor treatment[a].

Variable	Case A Pre-Ivacaftor	Case A 6 weeks post	Case A 12 weeks post	Case B Pre-Ivacaftor	Case B 6 weeks post	Case B 12 weeks post
Clinical outcomes	-	-	-	-	-	-
FEV_1 [$L \cdot min^{-1}$ (%predicted)]	2.53 (92)	2.62 (96)	2.65 (97)	4.19 (108)	4.33 (112)	4.65 (120)
FVC [$L \cdot min^{-1}$ (%predicted)]	3.20 (100)	3.36 (105)	3.32 (107)	4.86 (104)	4.59 (98)	4.98 (106)
FEF_{25-75} [$L \cdot min^{-1}$ (%predicted)]	2.29 (66)	2.38 (67)	2.52 (71)	4.77 (106)	5.08 (113)	5.41 (120)
Sweat chloride concentration	104	21	35	107	58	43
($mmol \cdot L^{-1}$)	-	-	-	-	-	-
Body mass (kg)	48.5	50.5	50.2	58.3	58.3	58.8
Stature (cm)	154.8	155.0	155.0	172.0	172.0	172.2
Maximal exercise parameters	-	-	-	-	-	-
Absolute $\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	1.45	1.60	1.95	2.59	2.60	2.44
Relative $\dot{V}O_{2max}$	29.42	31.30	38.33	44.20	45.72	41.93
($mL \cdot kg^{-1} \cdot min^{-1}$)	-	-	-	-	-	-
HR_{max} ($beats \cdot min^{-1}$)	205	202	202	198	195	175
SV_{max} (mL)	52.4	56.2	60.3	83.9	89.2	104.2
$\dot{Q}_{max}$ ($L \cdot min^{-1}$)	10.6	10.8	11.6	19.0	15.5	18.2
a-$\dot{V}O_2$ diff. ($mL \cdot min^{-1} \cdot 100mL$)	13.7	14.8	16.8	13.6	16.8	13.4
Lowest SaO_2 (%)	92	96	98	96	96	98
RPE	10	9	9	9	9	9
RPD	7	6	5	7	7	9
Ramp peak power output (W)	136	129	148	220	225	240
Submaximal parameters	-	-	-	-	-	-
$\dot{V}O_2$ at the GET ($L \cdot min^{-1}$)	0.87	0.85	0.87	1.32	1.28	1.09
%GET (% of $\dot{V}O_{2max}$)	60.12	52.99	44.55	51.05	54.78	44.72
$\Delta\dot{V}O_2/\Delta WR$ ($mL \cdot min^{-1} \cdot W^{-1}$)	7.20	8.00	7.40	9.32	8.46	6.52

[a]Values are means ± SD, with the range also displayed unless otherwise stated. Additional submaximal parameters are available upon request.

Abbreviations: % predicted, percentage predicted[17]; $C_{(a-v)}O_2$., arterial-venous O_2 content difference; $\dot{Q}_{max}$, maximal cardiac output; $\dot{V}O_{2max}$, maximal oxygen uptake; $\Delta\dot{V}O_2/\Delta WR$, oxygen cost of exercise ($\dot{V}O_2$ gain); FEF_{25-75}, mid forced expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced expiratory lung volume; GET, non-invasive estimate of the lactate threshold which was verified by the ventilatory threshold; HR_{max}, maximal heart rate; ramp; incremental ramp test; RPD, end-exercise rating of perceived dyspnea; RPE, end-exercise rating of perceived exertion; SpO_2, arterial oxygen saturation; SV_{max}, maximal stroke volume; URTI, upper respiratory tract infection.