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Short communication

Physiological mechanisms of dyspnea relief following ivacaftor in cystic fibrosis: A case report

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ABSTRACT

Ivacaftor is a novel oral pharmacologic agent that specifically targets the genetic defect of cystic fibrosis (CF) by augmenting chloride conductance through the CF transmembrane regulator (CFTR) protein. For individuals with CF and at least one copy of the G551D gating mutation, improvements in sweat chloride, nutritional parameters, lung function, respiratory symptoms, and exercise tolerance (i.e., 6-min walk distance) are attained within 2 weeks of initiating ivacaftor. However, there are no reports detailing the physiological and sensory implications of these improvements and their underlying mechanisms. We performed detailed cardiopulmonary exercise testing pre- and post-initiation of ivacaftor in a 27-year old male with CF (CFTR genotype F508del/G551D) and chronic airflow obstruction ($FEV_1/FVC = 0.44$). An improvement of FEV_1 (by 16%) following ivacaftor was accompanied by clinically significant improvements in exercise capacity (by 14%) and exertional dyspnea (by up to 5 Borg scale units). These improvements were attributable, at least in part, to favorable alterations in the ventilatory response to exercise, including improvements in breathing patterns (e.g., increased tidal volume and reduced breathing frequency) and dynamic operating lung volumes (e.g., increased inspiratory reserve volume and inspiratory capacity) and decreases in dynamic mechanical ventilatory constraints.

1. Introduction

The management of individuals with cystic fibrosis (CF) and a G551D gating mutation changed significantly in January 2012 when the FDA approved ivacaftor. Ivacaftor is an oral pharmacologic agent that acts on the underlying genetic defect in CF by potentiating chloride conductance through the CF transmembrane regulator (CFTR) protein. Enhanced chloride conductance in patients with this gating mutation restores airway surface liquid and improves mucociliary clearance. Studies have reported clinically significant improvements in lung function, respiratory symptoms, body mass, and sweat chloride in both children (6 years and older) and adults within 2 weeks of initiating ivacaftor (Davies et al., 2013; Ramsey et al., 2011). Previous case reports have highlighted reductions in airway thickening and mucus plugging via computed tomography (CT) (Hoare et al., 2014) and improvements in 6-min walk distance (Harrison et al., 2013). However, the present case report is the first to describe the potential physiological and sensory implications of these improvements and their underlying mechanisms during cardiopulmonary exercise testing.

2. Case report and methods

We report the impact of ivacaftor (150 mg administered orally twice daily) on the exercise capacity, exertional symptoms, and respiratory physiological responses to exercise in a 27-year old male with CF (CFTR genotype F508del/G551D) and chronic airflow obstruction (forced expiratory volume in 1 s (FEV_1) = 39% predicted). The patient provided informed written consent for this case report. He had a significantly diminished baseline peak oxygen uptake (46% predicted) and experienced severe chronic activity related dyspnea (modified Medical Research Council (mMRC) rating 3). This patient participated in a comprehensive clinical exercise physiology study 2 weeks prior to initiation of ivacaftor.

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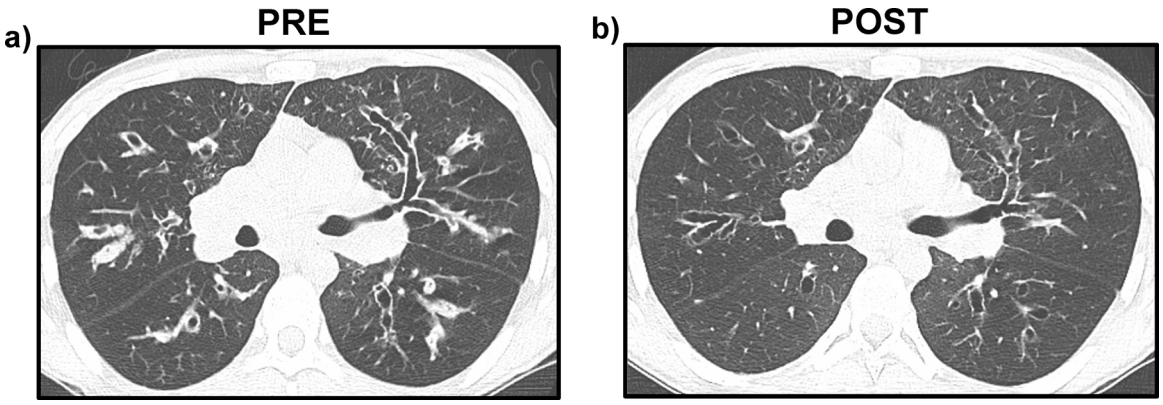

Fig. 1. Non-contrast computed tomography scans obtained (a) pre, and (b) post ivacaftor treatment demonstrates an improvement in bronchial wall thickening and mucus plugging.

The study involved detailed measures of pulmonary function (spirometry, plethysmography, lung diffusion capacity for carbon monoxide, and maximal inspiratory and expiratory pressures) and a symptom-limited incremental cardiopulmonary exercise test using an electronically braked cycle ergometer according to recommended guidelines (ATS, 2003). Serial inspiratory capacity maneuvers were performed throughout exercise and a careful assessment of expiratory flow limitation (EFL) was performed using previously described methods (Guenette et al., 2010). Both the intensity and qualitative dimensions of dyspnea were monitored throughout exercise as described elsewhere (Laveneziana et al., 2013, 2011). Briefly, the patient was asked to rate the intensity of his "breathing discomfort" and "leg discomfort" using the modified 10-point Borg scale at rest and during each 2 min stage of exercise. The patient also selected phrases that best described his breathing immediately following the dyspnea intensity ratings: (1) "My breathing requires more work and effort" (work and effort); (2) "I cannot get enough air in" (unsatisfied inspiration); and (3) "I cannot get enough air out" (unsatisfied expiration). The patient returned to the laboratory 8 weeks following the initiation of ivacaftor where he underwent identical testing procedures. CT scans were obtained as part of routine assessment 13 months prior to initiation of ivacaftor and 10 weeks following initiation to monitor treatment response.

3. Results

Post-ivacaftor CT scan demonstrated a marked reduction in bronchial wall thickening and mucus plugging (Fig. 1a and b). The mMRC dyspnea score decreased from 3 to 1 indicating a substantial improvement in his chronic activity-related dyspnea. His degree of airflow obstruction, gas trapping, gas transfer, body mass, respiratory muscle strength, and sweat choloride improved following treatment (Table 1). Exercise duration, absolute peak work rate, and absolute peak oxygen uptake increased by 33%, 25%, and 14%, respectively (Table 1). Ventilatory efficiency (V_E/VCO_2 slope) improved by 9%. Dyspnea intensity ratings were markedly reduced at standardized absolute work rates; for example, by 2 and 5 Borg scale units at 60 and 80 W, respectively (Fig. 2a). The dominant qualitative descriptor of dyspnea prior to treatment was a heightened sensation of "unsatisfied inspiration" at work rates above 40 W. In contrast, following treatment, dyspnea was described as a heightened sense of increased "work/effort" at all submaximal work rates. Similar to the dyspnea intensity ratings, perceived leg

Table 1
Subject characteristics pre- and post-treatment with ivacaftor.

	Pre-ivacaftor	Post-ivacaftor	% change
mMRC dyspnea	3	1	−67
Mass, kg	55.8	60.5	+8
BMI, kg/m^2	16.7	18.1	+8
Sweat chloride, mmol/L	104	62	−40
FEV_1, L	1.89 (39)	2.19 (46)	+16
FVC, L	4.27 (73)	4.58 (78)	+7
TLC, L	7.91 (101)	8.01 (102)	+1
SVC, L	4.30 (70)	4.82 (79)	+12
FRC, L	5.83 (154)	5.84 (154)	0
RV, L	3.61 (202)	3.19 (178)	−12
DL_{CO}, mL/mmHg/min	21.6 (53)	26.3 (65)	+22
MIP, cmH_2O	85(66)	94(73)	+11
MEP, cmH_2O	106(44)	119(49)	+12
Exercise time, min	7.5	10	+33
Peak work rate, watts	80	100	+25
VO_{2peak}, L/min	1.52 (46)	1.73 (52)	+14
VO_{2peak}, mL/kg/min	27.2	28.6	+5
Work rate, watts	80	100	+25
Work rate, watts/kg	1.4	1.7	+15
IRV_{peak}, mL	382	437	+14
V_E/VCO_2 slope	33	30	−9

Values reported as absolute values (% predicted). *Abbreviations*: mMRC, modified medical research council; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; SVC, slow vital capacity; FRC, functional residual capacity; RV, residual volume; DL_{CO}, lung diffusing capacity for carbon monoxide; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; VO_{2peak}, peak oxygen consumption; IRV_{peak}, peak exercise inspiratory reserve volume; V_E, minute ventilation; VCO_2, carbon dioxide production.

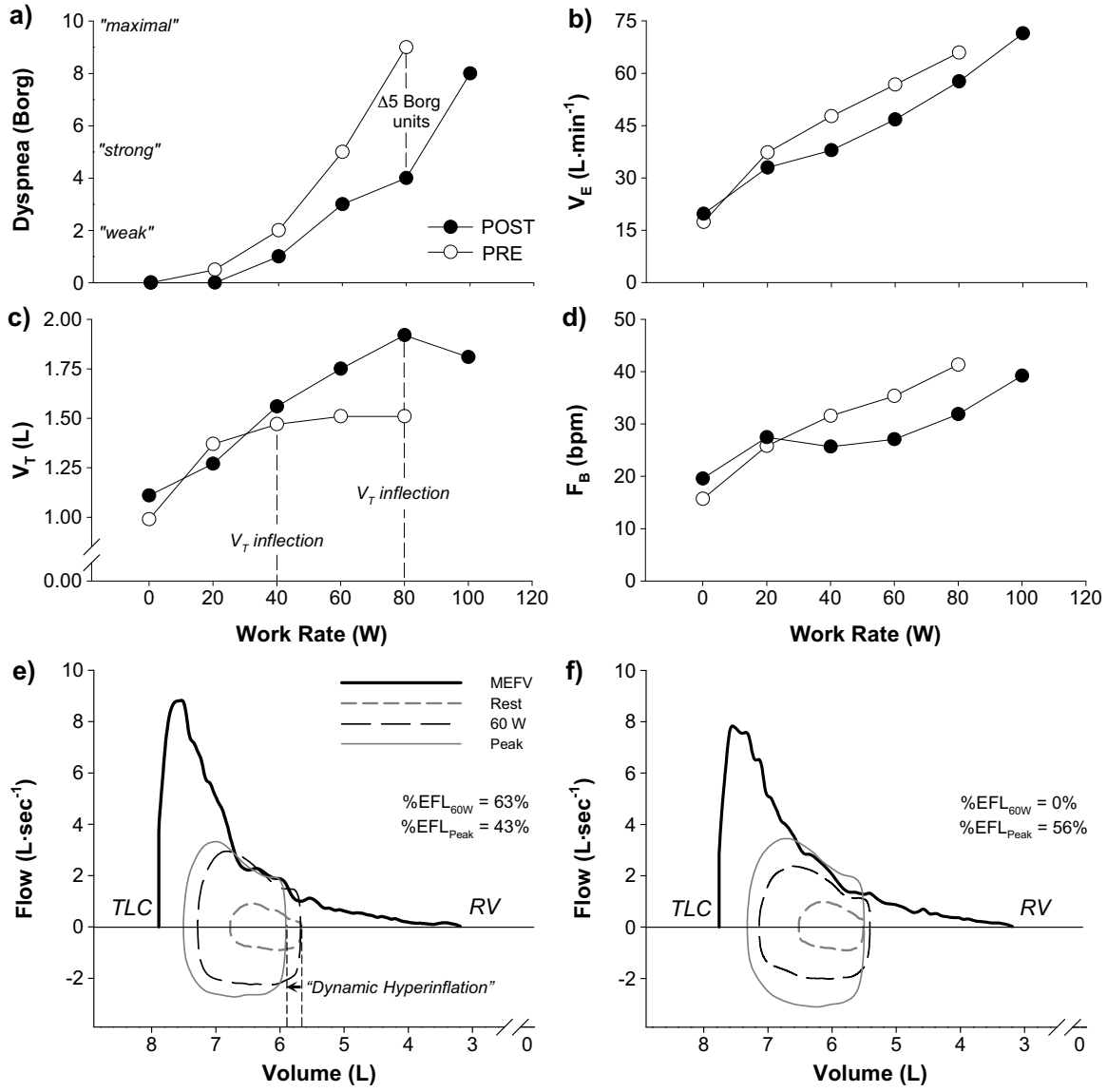

Fig. 2. Changes in (a) dyspnea intensity, (b) minute ventilation (V_E), (c) tidal volume (V_T), and (d) breathing frequency (F_B) are shown relative to work rate in response to incremental cycle exercise pre- and post-treatment with ivacaftor. Maximal expiratory flow–volume (MEFV) curves and tidal flow–volume loops at rest, 60 W and peak exercise obtained during incremental cycle exercise tests are shown (e) before and (f) after treatment. The percent magnitude of expiratory flow limitation (%EFL) was determined by taking the volume of the expired tidal breath that overlapped the maximum expiratory flow–volume curve and dividing it by the tidal volume of that breath. TLC, total lung capacity; RV, residual volume.

discomfort was also reduced during exercise by 4 and 5 Borg scale units at 60 and 80 W, respectively.

Following treatment, minute ventilation (V_E) was consistently reduced for any given submaximal work rate and this was achieved using a less rapid and shallow breathing pattern (Fig. 2b–d). These improvements may reflect, at least in part, increases in inspiratory capacity and the inspiratory reserve volume, both of which increased by an average of 141 and 150 mL, respectively, at rest and throughout exercise. The modest increase in inspiratory muscle strength by 11% (Table 1) may account for some of the observed improvement in the inspiratory capacity. Flow-volume loop analysis revealed a number of additional improvements in the ventilatory response to exercise (Fig. 2e and f). Notably, prior to treatment with ivacaftor, the patient developed significant EFL (i.e., 63% of the tidal breath was flow limited) while exercising at 60 W, resulting in dynamic hyperinflation during the subsequent exercise stage (80 W) by 241 mL. Following treatment, EFL was abolished at 60 W with no hyperinflation at 80 W or at peak exercise. The reduction in EFL at submaximal work rates reflected a combination of reduced ventilatory requirements and increases in the capacity to generate expired flow at a given lung volume (i.e., forced expiratory flows between 25 and 75% of vital capacity increased by 21%). The magnitude of EFL was slightly higher at peak exercise following ivacaftor, likely reflecting the higher maximal V_E achieved following treatment.

4. Discussion

This is the first report showing the physiological mechanisms of improvement in dyspnea and exercise tolerance following treatment with a novel therapeutic agent that acts on the underlying defect in CF with a G551D gating mutation. Our results demonstrate that ivacaftor leads to substantial improvements in baseline pulmonary function which translates directly into improvements in the ventilatory and sensory responses to symptom limited cardiopulmonary exercise testing.

Recent work has highlighted the importance of the tidal volume (V_T) inflection during exercise in patients with varying degrees of airflow obstruction (O'Donnell et al., 2012). This critical mechanical event is typically associated with a rapid increase in dyspnea intensity to intolerable levels. Our patient achieved an inflection in V_T at a V_E of 42 L/min and a work rate of 40 W prior to treatment with ivacaftor. Following treatment, the V_T inflection occurred at a higher V_E (53 L/min) and work rate (80 W) as depicted in Fig. 2c. In both exercise tests, dyspnea intensity rose abruptly at the V_T inflection. This critical mechanical event also marked the transition where the dominant qualitative descriptor of dyspnea changed from "work and effort" to "unsatisfied inspiration", a finding consistent with studies in COPD (Laveneziana et al., 2011) and asthma (Laveneziana et al., 2013). Thus, the delay of critical ventilatory constraints in our patient allowed him to experience less intense dyspnea and a less distressing form of this sensation for a given submaximal cycle work rate. Interestingly, our patient also experienced a marked improvement in perceived leg discomfort throughout exercise. Although our patient was not participating in structured exercise training throughout the study period, he did comment that we was walking more and that it was easier for him to perform his activities of daily living during treatment. Thus, it is possible that the improvements observed in exercise capacity may reflect, at least in part, unmeasured improvements in daytime physical activity levels with attendant improvements in cardiovascular fitness, peripheral locomotor muscle strength/endurance, and body composition (e.g., increase in % of lean tissue mass).

The reduction in ventilatory demands coupled with the attenuation (and delayed onset) of ventilatory constraints likely led to a reduction in central motor output needed to drive the respiratory muscles for any given exercise intensity. We speculate that this reduction in respiratory drive combined with improvements in the mechanical output of the respiratory system and increases in respiratory muscle strength resulted in greater neuromechanical coupling of the respiratory system. Although further research is required, this likely forms the mechanistic basis for the improvements in both the intensity and qualitative dimensions of exertional dyspnea in our patient following treatment with ivacaftor (O'Donnell et al., 2009).

5. Conclusion

The results of this case report demonstrate that augmentation of mucociliary clearance leads to an improvement in exercise capacity and favorable alterations in both the intensity and qualitative dimensions of exertional dyspnea in CF. The improvement in resting airflow obstruction and reduction in gas trapping had direct beneficial effects on the ventilatory response to exercise. Decreases in ventilatory requirements coupled with a more mechanically efficient breathing pattern played an important role in reducing dyspnea and improving exercise tolerance in our patient. This case study provides the rationale for future studies examining the role of exercise testing as an ancillary biomarker to assess the efficacy of ivacaftor on important clinical, physiological and patient-reported outcomes in selected patients with CF.

Conflicts of interest

BSQ, MRS, YMS, SSW and JAG do not have any conflicts of interest to report relevant to this manuscript. PGW has been a site principal investigator on multicentre clinical trials sponsored by Vertex Pharmaceuticals.

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